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(54) **Title:** COMPOSITION AND ANTIVIRAL ACTIVITY OF SUBSTITUTED INDOLEOXOACETIC PIPERAZINE DERIVATIVES

(57) **Abstract:** This invention provides compounds having drug and bio-affecting properties, their pharmaceutical compositions and mthod of use. In particular, the invention is converned with indoleoxoacetyl piperazine derivatives. These compounds possess unique antiviral activity, whether used alone or in combination with other antivirals, antiinfectives, immunomodulators or HIV entry inhibitors. Mor particularly, the present invention relates to the treatment of HIV and AIDS.

COMPOSITION AND ANTIVIRAL ACTIVITY OF SUBSTITUTED INDOLEOXOACETIC PIPERAZINE DERIVATIVES

5   ## BACKGROUND OF THE INVENTION

Field of the Invention

This invention provides compounds having drug and bio-affecting properties, their pharmaceutical compositions and method of use. In
10   particular, the invention is concerned with indoleoxoacetyl piperazine derivatives. These compounds possess unique antiviral activity. More particularly, the present invention relates to the treatment of HIV and AIDS.

Background Art

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HIV-1 (human immunodeficiency virus -1) infection remains a major medical problem, with an estimated 33.4 million people infected worldwide. Currently available HIV drugs include six nucleoside reverse transcriptase (RT) inhibitors (zidovudine, didanosine, stavudine, lamivudine, zalcitabine
20   and abacavir), three non-nucleoside reverse transcriptase inhibitors (nevirapine, delavirdine and efavirenz) as well as five peptidomimetic protease inhibitors (saquinavir, indinavir, ritonavir, nelfinavir and amprenavir). Each of these drugs can only transiently restrain viral replication if used alone. However, when used in combination, these drugs have a profound
25   effect on disease progression. In fact, significant reductions in death rates among AIDS patients have been recently documented. Despite these results, 30 to 50% of patients ultimately fail combination drug therapies. Insufficient drug potency, non-compliance, restricted tissue penetration and drug-specific limitations within certain cell types (e.g. most nucleoside
30   analogs cannot be phosphorylated in resting cells) may account for the incomplete suppression of sensitive viruses. Furthermore, the high replication rate and rapid turnover of HIV-1 combined with the frequent incorporation of mutations, leads to the appearance of drug-resistant variants and treatment failures when suboptimal drug concentrations are present
35   (Larder and Kemp, Gulick, Morris-Jones, et al, Kuritzkes, Vacca and Condra,

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Schinazi, et al and Flexner, Ref. 6-12). Therefore, novel anti-HIV agents exhibiting distinct resistance patterns, and favorable pharmacokinetic as well as safety profiles are needed to provide more treatment options.

5   Currently marketed HIV-1 drugs are dominated by either nucleoside reverse transcriptase inhibitors or peptidomimetic protease inhibitors. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have recently gained an increasingly important role in the therapy of HIV infections. At least 30 different classes of NNRTIs have been published in the literature (DeClercq,
10   Ref. 13). Dipyridodiazepinone (nevirapine), benzoxazinone (efavirenz) and bis(heteroaryl) piperazine derivatives (delavirdine) are already approved for clinical use. In addition, several indole derivatives including indole-3-sulfones, piperazino indoles, pyrazino indoles, and 5H-indolo[3,2-b][1,5]benzothiazepine derivatives have been reported as HIV-1 reverse
15   transciptase inhibitors (Greenlee et al, Ref. 1, Williams et al, Ref. 2, Romero et al, Ref. 3, Font et al, Ref. 14, Romero et al, Ref. 15, Young et al, Ref. 16, Genin et al, Ref. 17, and Silvestri et al, Ref. 18). Other indole derivatives exhibiting antiviral activity useful for treating HIV are disclosed in PCT WO 00/76521, Ref. 102). Also, indole derivatives are disclosed in PCT WO
20   00/71535, Ref. 103. Indole 2-carboxamides have also been described as inhibitors of cell adhesion and HIV infection (Boschelli et al. in US 5,424,329, Ref. 4). Finally, 3-substituted indole natural products (Semicochliodinol A and B, didemethylasterriquinone and isocochliodinol) were disclosed as inhibitors of HIV-1 protease (Fredenhagen et al, Ref. 19). However, nothing
25   in these references can be construed to disclose or suggest the novel compounds of this invention and their use to inhibit viral infections, including HIV infection.

           Structurally related compounds have been disclosed previously
30   (Brewster et al, Ref. 20, Archibald et al, Ref. 21, American Home Products in GB 1126245, Ref. 5). However, the structures differ from those claimed herein in that they are symmetrical bis(3-indolylglyoxamides) rather than unsymmetrical aroyl indoleoxoacetyl piperazine derivatives, and there is no mention of use for treating viral infections. Interestingly, the indole moiety
35   present in the compounds disclosed here is the common feature of many non-nucleoside HIV-1 reverse transcriptase inhibitors including Delavirdine from Upjohn (Dueweke et al. 1992, 1993, Ref. 22 and 23).

A recent PCT application, WO 99/55696, described substituted indoles as phosphodiester 4 inhibitors.
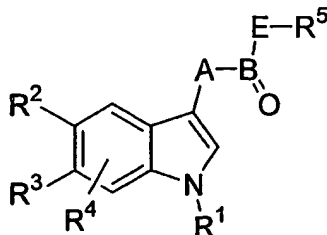
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SUMMARY OF THE INVENTION

The present invention comprises compounds of Formula I, their pharmaceutical formulations, and their use in patients suffering from or susceptible to a virus such as HIV. The compounds of Formula I which include nontoxic pharmaceutically acceptable salts and/or hydrates thereof have the formula and meaning as described below.

A first embodiment of a first aspect of the present invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,
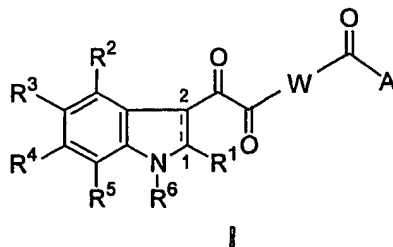
wherein:

A is selected from the group consisting of C_{1-6}alkoxy, aryl and heteroaryl; in which said aryl is phenyl or napthyl; said heteroaryl is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, furanyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, benzoimidazolyl and benzothiazolyl; and said aryl or heteroaryl is optionally substituted with one or two of the same or different amino, nitro, cyano, C_{1-6}alkoxy, $-C(O)NH_2$, halogen or trifluoromethyl;

-W- is
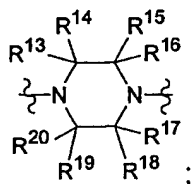
- - may represent a carbon-carbon bond; (i.e. when - - represents a carbon-carbon bond the carbons denoted 1 and 2 are attached to each other by a carbon-carbon double; when - - does not represent a carbon-carbon bond then the carbons denoted 1 and 2 are attached to each other by a carbon-carbon single bond);

R^1 is hydrogen;

R^2, R^3, R^4, and R^5 are each independently selected from the group (a)-(r) consisting of:

(a) hydrogen,

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(b) halogen,

(c) cyano,

(d) nitro,

(e) amino,

(f) C_{1-4}alkylamino,

(g) di(C_{1-4}alkyl)amino,

(h) hydroxy,

(i) C_{1-6}alkyl optionally substituted with one to three same or different halogen, hydroxy, C_{1-6}alkoxy, amino, C_{1-4}alkylamino, di (C_{1-4}alkyl)amino, cyano or nitro,   .

(j) C_{3-7}cycloalkyl optionally substituted with one to three same or different halogen, hydroxy, C_{1-6}alkoxy, amino, C_{1-4}alkylamino, di   . (C_{1-4}alkyl)amino, cyano or nitro,

(k) C_{1-6}alkoxy,

(l) $-C(O)OR^7$,

(m) $-C(O)R^8$,

(n) $-C(O)NR^9R^{10}$,

(o) $-C(=NR^{12})(R^{11})$,

(p) aryl, said aryl is phenyl or napthyl, and said aryl is optionally substituted with one to two of the same or different amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, cyano, C-amido, N-amido, C_{1-6} alkoxy, C_{1-6}thioalkoxy or halogen,

(q) heteroaryl, said heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl, and said heteroaryl is optionally substituted with one to two same or different groups selected from (aa)-(pp) consisting of: (aa) halogen, (bb) C_{1-6} alkyl, said C_{1-6} alkyl optionally substituted with one to three same or different halogen, hydroxy, cyano, amino, C_{1-4}alkylamino or di(C_{1-4}alkyl)amino, (cc) C_{3-6}alkenyl, (dd) C_{1-6}alkoxy, (ee) phenyl optionally substituted with one or two same or different halogen, (ff) heteroaryl, said heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, furanyl, thienyl, oxazolyl, isoxazolyl, pyrazolyl, triazolyl and tetrazolyl, and said heteroaryl optionally substituted with one or two same or different C_{1-4}alkyl, C_{1-4}alkoxy,

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halogen, amino, C_{1-4}alkylamino and di(C_{1-4}alkyl)amino, (gg) heteroarylC_{1-6}alkyl-, in which the heteroaryl of said heteroaryl C_{1-6}alkyl- is selected from the group consisting of pyridinyl, furanyl, thienyl and pyrazolyl, the heteroaryl of said heteroarylC_{1-6}alkyl- is

5   optionally substituted with one or two same or different C_{1-4}alkyl, halogen or amino, and in which a carbon of the C_{1-6}alkyl of said heteroarylC_{1-6}alkyl- is optionally replaced by one sulfur or sulfonyl, (hh) amino, (ii) C_{1-4}alkylamino, in which the C_{1-4}alkyl of said C_{1-4}alkylamino is optionally substituted with amino, C_{1-4}alkylamino,

10   di(C_{1-4}alkyl)amino, morpholinyl, piperazinyl or piperidinyl, (jj) di (C_{1-4}alkyl)amino, (kk) C_{3-7}cycloalkylamino, (ll) -$(CH_2)_q{}^aC(O)R^{23}$, (mm) -$CH_2OC(O)C_{1-6}$alkyl, (nn) -NH-$(CH_2)_q{}^bC(O)R^{24}$, (oo) -$CO_2CH_2C(O)R^{25}$, (pp) phenylmethyl, in which the phenyl of said phenylmethyl is optionally substituted with a -$(CH_2)_q{}^cC(O)R^{26}$; and

15 (r) heteroalicyclic, said heteroalicyclic selected from the group consisting of piperazinyl, piperidinyl, morpholinyl, 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, 4,5-dihydro-thiazol-2-yl, 5-oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl and 4,5-dihydro-1H-imidazol-2-yl, and said heteroalicyclic is optionally substituted with one or two same

20   or different C_{1-4}alkyl, C_{1-4}alkoxy, hydroxy, cyano or amino;

R^6 and R^7 are each independently selected from hydrogen or C_{1-6} alkyl;

25 R^8 is selected from the group consisting of C_{1-6}alkyl, phenyl and heteroaryl in which said heteroaryl is selected from the group consisting of oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, and pyrimidinyl and said heteroaryl is optionally substituted with one to two of the same or different C_{1-6}alkyl, amino, CO_2H or

30 CO_2C_{1-6}alkyl;

R^9 and R^{10} are each independently selected from the group (a)-(l) consisting of:

(a) hydrogen,

35   (b) C_{1-6}alkyl, said C_{1-6}alkyl is optionally substituted with in one to two of the same or different amino, di(C_{1-6}alkyl)amino or C_{1-6}alkoxy,

(c) C_{1-6}alkoxy,

    (d) heteroaryl, in which said heteroaryl is selected from the group consisting of pyridinyl, isoxazolyl, benzoimidazolyl, tetrazolyl, pyrazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, benzothiazolyl, pyrimidinyl and isoquinolinyl and said heteroaryl is optionally substituted with one to two of the same or different C_{1-6}alkyl or C_{1-6}alkoxy,

    (e) heteroaryl-C_{1-6}alkyl-, in which said heteroaryl is selected from the group consisting of indolyl, imidazolyl, benzoimidazolyl, pyridinyl, pyrimidinyl, thiazolyl, triazolyl, tetrazolyl, furanyl and thienyl,

    (f) heteroalicyclic, in which said heteroalicyclic is morpholinyl, piperazinyl or dihydrothiazolyl, and said heteroalicyclic is optionally substituted with a C_{1-6}alkoxycarbonyl,

    (g) morpholin-4-ylethyl,

    (h) phenylsulfonyl,

    (i) C_{1-4}alkylsulfonyl,

    (j) amino,

    (k) (C_{1-6}alkoxy)-C(O)NH-, and

    (l) (C_{1-6}alkyl)-NHC(O)NH; or R^9 and R^{10} taken together with the nitrogen to which they are attached are 4-benzylpiperazin-1-yl or 4-benzoylpiperazin-1-yl;

R^{11} is selected from the group consisting of hydrogen, C_{1-6}alkoxy and $NR^{21}R^{22}$;

R^{12} is selected from the group consisting of hydrogen, hydroxy, $NHCO_2$ C_{1-6}alkyl and C_{1-6}alkoxy, said C_{1-6}alkoxy optionally substituted with one CO_2H or CO_2C_{1-6}alkyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} are each independently selected from hydrogen or C_{1-6}alkyl;

R^{21} and R^{22} are each independently selected from the group consisting of hydrogen, amino, C_{1-6}alkyl, C_{3-7}cycloalkyl and $NHCO_2C_{1-6}$alkyl;

R^{23}, R^{24}, R^{25} and R^{26} are each independently selected from the group consisting of hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy optionally substituted with morpholin-4-yl or di(C_{1-4}alkyl)amino, amino, pyrolidin-1-yl, (C_{1-4}alkyl)amino and di(C_{1-4}alkyl)amino;

q^a, q^b and q^c are each independently 0 or 1; and

provided that at least one of R^2, R^3, R^4, and R^5 is selected from the group
consisting of -C(O)R^8, -C(O)NR^{9}R^{10}, -C(=NR^{12})(R^{11}), aryl, heteroaryl, and
heteroalicyclic when - - represents a carbon-carbon bond.

A second embodiment of the first aspect of the present invention is a
compound of the first embodiment of the first aspect, including
pharmaceutically acceptable salts thereof wherein: A is selected from the
group consisting of C$_{1-6}$alkoxy, phenyl and heteroaryl in which said
heteroaryl is selected from pyridinyl, furanyl and thienyl, and said phenyl or
said heteroaryl is optionally substituted with one to two of the same or
different amino, nitro, cyano, C$_{1-6}$alkoxy, -C(O)NH$_2$, halogen or trifluoromethyl;
- - represents a carbon-carbon bond; R^8 is hydrogen; R^{13}, R^{14}, R^{16}, R^{17} and
R^{18} are each hydrogen; and R^{15}, R^{19} and R^{20} are each independently
hydrogen or C$_{1-6}$alkyl.

A third embodiment of the first aspect of the present invention is a
compound of the second embodiment of the first aspect or a
pharmaceutically acceptable salt thereof, wherein: R^2 is selected from the
group consisting of hydrogen, halogen and C$_{1-6}$alkoxy; R_3 and R_4 are
hydrogen; and R^5 is selected from the group consisting of: -C(O)R^8,
-C(O)NR^{9}R^{10}, -C(=NR^{12})(R^{11}), aryl, heteroaryl and heteroalicyclic.

A fourth embodiment of the first aspect of the present invention is a
compound of the third embodiment of the first aspect or a pharmaceutically
acceptable salt thereof, wherein: R^2 is halogen or C$_{1-6}$alkoxy; R^5 is phenyl,
said phenyl optionally substituted with a C$_{1-4}$alkoxy, C$_{1-4}$thioalkoxy or halogen;
R^{15} and R^{19} are each hydrogen; R^{20} is hydrogen or methyl; and A is phenyl.

A fifth embodiment of the first aspect of the present invention is a
compound of the fourth embodiment of the first aspect wherein: R^2 is fluoro or
methoxy; R^5 is phenyl, said phenyl optionally substituted with a methoxy,
thiomethoxy, or fluoro; and R^{20} is hydrogen.

A sixth embodiment of the first aspect of the present invention is a
compound of the third embodiment of the first aspect or a pharmaceutically

acceptable salt thereof, wherein: R^2 is halogen or C_{1-6}alkoxy; R^5 is selected from the group consisting of -C(O)NR^{9}R^{10}, -C(=NR^{12})(R^{11}) and heteroaryl in which said heteroaryl is tetrazolyl or oxadiazolyl and said heteroaryl is optionally substituted with one to two C_{1-6}alkyl, dihalomethyl, trihalomethyl or halogen; R^{15} and R^{19} are each hydrogen; R^{20} is hydrogen or C_{1-6} alkyl; and A is heteroaryl, said heteroaryl selected from the group consisting of pyridinyl, furanyl and thienyl and said heteroaryl optionally substituted with a halogen.

A seventh embodiment of the first aspect of the present invention is a compound of the sixth embodiment of the first aspect wherein: R^2 is fluoro; R^5 is selected from the group consisting of 2H-tetrazolyl, 2-dihalomethyl-2H-tetrazolyl, [1,2,4]-oxadiazolyl, 5-amino-[1,2,4]-oxadiazolyl, 5-trihalomethyl-[1,2,4]-oxadiazolyl, -C(O)NH$_2$ and –C(=NOH)NH$_2$; R^{20} is hydrogen or methyl; and A is pyridinyl.

A eighth embodiment of the first aspect of the present invention is a compound of the sixth embodiment of the first aspect wherein: R^2 is fluoro; R^5 is 2H-tetrazolyl or 2-methyl-2H-tetrazolyl; R^{20} is hydrogen; and A is furanyl or thienyl, in which said furanyl is optionally substituted with a chloro or bromo.

A ninth embodiment of the first aspect of the present invention is a compound of the third embodiment of the first aspect wherein: R^2 is selected from the group consisting of hydrogen, fluoro or methoxy; R^5 is -C(O)NR^{9}R^{10}; R^{15} and R^{19} are each hydrogen; R^{20} is hydrogen or methyl; and A is phenyl.

A tenth embodiment of the first aspect of the present invention is a compound of the ninth embodiment of the first aspect wherein: R^2 is hydrogen; and R^9 and R^{10} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl optionally substituted with a di (C$_{1-4}$alkyl)amino, methylsulfonyl, phenylsulfonyl, and tetrazolyl, or R^9 and R^{10} taken together with the nitrogen to which they are attached are 4-benzylpiperazin-1-yl.

An eleventh embodiment of the first aspect of the present invention is a compound of the ninth embodiment of the first aspect wherein R^2 is methoxy; R^{20} is hydrogen; and R^9 and R^{10} are each independently hydrogen or methyl.

A twelth embodiment of the first aspect of the present invention is a compound of the ninth embodiment of the first aspect wherein: R^2 is fluoro; R^{20} is methyl; and R^9 and R^{10} are each independently selected from the group consisting of hydrogen, C_{1-6}alkyl and morpholin-4-ylethyl.

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selected from the group consisting of hydrogen, methoxy and fluoro; R^5 is heteroalicyclic, said heteroalicyclic selected from the group consisting of 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, 4,5-dihydro-thiazol-2-yl, 5-oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl and 4,5-dihydro-1H-imidazol-2-yl; R^{15} and R^{19}

5   are each hydrogen; R^{20} is hydrogen or methyl; and A is phenyl.

A twentieth embodiment of the first aspect of the present invention is a compound of the third embodiment of the first aspect wherein: R^2 is selected from the group consisting of hydrogen, methoxy and fluoro;

10   R^5 is -C(=NR^{12})(R^{11}); A is phenyl or C_{1-6}alkoxy; R^{11} is selected from the group consisting of hydrogen, hydroxy, $NHCO_2C(CH_3)_3$ and OCH_2CO_2H; and R^{12} is selected from the group consisting of hydrogen, ethoxy and $NR^{21}R^{22}$; R^{15} and R^{19} are each hydrogen; R^{20} is hydrogen or methyl; and
       R^{21} and R^{22} are each independently selected from the group consisting of

15   hydrogen, amino, C_{1-6}alkyl, cyclopropyl and $NHCO_2C(CH_3)_3$.

A twentyfirst embodiment of the first aspect of the present invention is a compound selected from the group consisting of:

20   1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-oxazol-5-yl-1H-indol-3-yl)-ethane-1,2-dione;
       1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-[4-fluoro-7-(2H-tetrazol-5-yl)-1H-indol-3-yl]-ethane-1,2-dione;
       3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic

25   acid amide;
       3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid thiazol-2-ylamide;
       3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-1H-indole-7-carboxylic acid (1H-tetrazol-5-yl)-amide;

30   3-[2-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]-1H-indole-7-carboxylic acid methylamide;
       3-[2-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]-1H-indole-7-carboxylic acid dimethylamide;
       1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-methyl-2H-[1,2,4]triazol-3-yl)-1H-

35   indol-3-yl]-ethane-1,2-dione;
       1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-[1,2,4]oxadiazol-3-yl-1H-indol-3-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-(5-methyl-[1,2,4]oxadiazol-3-yl)-1H-indol-3-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[7-(5-cyclopropylamino-[1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

5   1-(4-Benzoyl-piperazin-1-yl)-2-[7-(5-amino-[1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(3H-imidazol-4-yl)-1H-indol-3-yl]-ethane-1,2-dione

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-[1,3,4]oxadiazol-2-yl-1H-indol-3-

10 yl)-ethane-1,2-dione;

1-[7-(5-Amino-[1,3,4]oxadiazol-2-yl)-4-fluoro-1H-indol-3-yl]-2-(4-benzoyl-piperazin-1-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(1H-[1,2,4]triazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

15 1-(4-Benzoyl-piperazin-1-yl)-2-[4-methoxy-7-(1H-[1,2,4]triazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-pyrazol-1-yl-1H-indol-3-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-imidazol-1-yl-1H-indol-3-yl)-ethane-

20 1,2-dione;

1-(7-Acetyl-4-methoxy-1H-indol-3-yl)-2-(4-benzoyl-piperazin-1-yl)-ethane-1,2-dione;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-methoxy-1H-indole-7-carboxylic acid amide;

25 1-(4-Fluoro-7-[1,2,4]oxadiazol-3-yl-1H-indol-3-yl)-2-[4-(3-nitro-benzoyl)-piperazin-1-yl]-ethane-1,2-dione;

1-[4-(3-Amino-benzoyl)-piperazin-1-yl]-2-(4-fluoro-7-[1,2,4]oxadiazol-3-yl-1H-indol-3-yl)-ethane-1,2-dione;

. 1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-[7-(5-cyclobutylamino-

30 [1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-(4-fluoro-7-[1,2,4]oxadiazol-3-yl-1H-indol-3-yl)-ethane-1,2-dione;

3-[2-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid amide;

35 1-[7-(5-Amino-[1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-2-[4-(pyridine-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione; and

1-(4-Fluoro-7-[1,2,4]oxadiazol-3-yl-1H-indol-3-yl)-2-[4-(pyridine-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione.

A first embodiment of a second aspect of the present invention is a pharmaceutical formulation which comprises an antiviral effective amount of a compound of Formula I, including pharmaceutically acceptable salts
5   thereof, and a pharmaceutically acceptable carrier, adjuvant or diluent.

A second embodiment of the second aspect of the present invention is a pharmaceutical formulation of a compound of Formula I, useful for treating a viral infection, such as HIV, which additionally comprises an antiviral
10   effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) HIV entry inhibitors.

A first embodiment of a third aspect of the present invention is a
15   method for treating mammals infected with or susceptible to a virus, comprising administering to said mammal an antiviral effective amount of a compound of Formula I as described previously for the first through twentyfirst embodiments of the first aspect, or a nontoxic pharmaceutically acceptable salt, solvate or hydrate thereof together with a conventional
20   adjuvant, carrier or diluent.

A second embodiment of the third aspect of the present invention is a method for treating mammals infected with a virus, wherein said virus is HIV, comprising administering to said mammal an antiviral effective amount of a
25   compound of Formula I.

A third embodiment of the third aspect of the present invention is a method for treating mammals infected with a virus, such as HIV, comprising administering to said mammal an antiviral effective amount of a compound of
30   Formula I in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) HIV entry inhibitors.

35   **DETAILED DESCRIPTION OF THE INVENTION**

The description of the invention herein should be construed in congruity with the laws and principals of chemical bonding.

DEFINITIONS

"Halogen" refers to chlorine, bromine, iodine or fluorine.

5

An "aryl" group refers to an all carbon monocyclic or fused-ring
polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups
having a completely conjugated pi-electron system. Examples, without
limitation, of aryl groups are phenyl, napthyl and anthracenyl. The aryl group
10   may be substituted or unsubstituted as specified. When substituted the
substituted group(s) is preferably one or more selected from alkyl, cycloalkyl,
aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy,
heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy,
thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, thiocarbonyl, O-
15   carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido,
C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido,
trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino,
ureido, phosphonyl, amino and -NR^{x}R^y, wherein R^x and R^y are independently
selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl,
20   alkynyl, aryl, carbonyl, C-carboxy, sulfonyl, trihalomethanesulfonyl,
trihalomethanecarbonyl, and, combined, a five- or six-member heteroalicyclic
ring.

As used herein, a "heteroaryl" group refers to a monocyclic or fused
25   ring (i.e., rings which share an adjacent pair of atoms) group having in the
ring(s) one or more atoms selected from the group consisting of nitrogen,
oxygen and sulfur and, in addition, having a completely conjugated pi-
electron system. Examples, without limitation, of heteroaryl groups are furyl,
thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl,
30   benzthiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl,
tetrahydropyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl,
purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl,
pyrazinyl, . When substituted the substituted group(s) is preferably one or
more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy,
35   alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy,
thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro,
carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-
thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy,

sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and -NR^{x}R^y, wherein R^x and R^y are as defined above.

5   As used herein, a "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of heteroalicyclic

10   groups are azetidinyl, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl and tetrahydropyranyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy,

15   thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and -NR^{x}R^y, wherein R^x and R^y

20   are as defined above.

An "alkyl" group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; e.g., "1-20", is stated

25   herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). For example, the term "C$_{1-6}$ alkyl" as used herein and in the claims (unless specified otherwise) mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl,

30   hexyl and the like. More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from trihaloalkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy,

35   thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido,

trihalomethanesulfonyl, and combined, a five- or six-member heteroalicyclic ring.

A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexadiene, cycloheptane, cycloheptatriene and adamantane. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroarylloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalo- methanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$ with R^x and R^y as defined above.

An "alkenyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond.

An "alkynyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond.

A "hydroxy" group refers to an $-OH$ group.

An "alkoxy" group refers to both an $-O$-alkyl and an $-O$-cycloalkyl group as defined herein.

An "aryloxy" group refers to both an $-O$-aryl and an $-O$-heteroaryl group, as defined herein.

A "heteroaryloxy" group refers to a heteroaryl-O- group with heteroaryl as defined herein.

A "heteroalicycloxy" group refers to a heteroalicyclic-O- group with heteroalicyclic as defined herein.

A "thiohydroxy" group refers to an –SH group.

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A "thioalkoxy" group refers to both an S-alkyl and an –S-cycloalkyl group, as defined herein.

A "thioaryloxy" group refers to both an –S-aryl and an –S-heteroaryl

10   group, as defined herein.

A "thioheteroaryloxy" group refers to a heteroaryl-S- group with heteroaryl as defined herein.

15   A "thioheteroalicycloxy" group refers to a heteroalicyclic-S- group with heteroalicyclic as defined herein.

A "carbonyl" group refers to a –C(=O)-R" group, where R" is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

20   heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), as each is defined herein.

An "aldehyde" group refers to a carbonyl group where R" is hydrogen.

25   A "thiocarbonyl" group refers to a –C(=S)-R" group, with R" as defined herein.

A "Keto" group refers to a –CC(=O)C- group wherein the carbon on either or both sides of the C=O may be alkyl, cycloalkyl, aryl or a carbon of a

30   heteroaryl or heteroaliacyclic group.

A "trihalomethanecarbonyl" group refers to a $Z_3CC(=O)$- group with said Z being a halogen.

35   A "C-carboxy" group refers to a –C(=O)O-R" groups, with R" as defined herein.

An "O-carboxy" group refers to a $R"C(-O)O$-group, with R" as defined herein.

A "carboxylic acid" group refers to a C-carboxy group in which R" is

5   hydrogen.

A "trihalomethyl" group refers to a $-CZ_3$, group wherein Z is a halogen group as defined herein.

10   A "trihalomethanecarbonyl" group refers to an $Z_3CC(=O)$- group with X as defined above.

A "trihalomethanesulfonyl" group refers to an $Z_3CS(=O)_2$- groups with Z as defined above.

15

A "trihalomethanesulfonamido" group refers to a $Z_3CS(=O)_2NR^x$- group with Z and R^x as defined herein.

A "sulfinyl" group refers to a $-S(=O)-R"$ group, with R" as defined

20   herein and, in addition, as a bond only; i.e., -S(O)-.

A "sulfonyl" group refers to a $-S(=O)_2R"$ group with R" as defined herein and, in addition as a bond only; i.e., $-S(O)_2-$.

25   A "S-sulfonamido" group refers to a $-S(=O)_2NR^xR^y$, with R^x and R^y as defined herein.

A "N-Sulfonamido" group refers to a $R"S(=O)_2NR_x$- group with R_x as defined herein.

30

A "O-carbamyl" group refers to a $-OC(=O)NR^xR^y$ as defined herein.

A "N-carbamyl" group refers to a $R^xOC(=O)NR^y$ group, with R^x and R^y as defined herein.

35

A "O-thiocarbamyl" group refers to a $-OC(=S)NR^xR^y$ group with R^x and R^y as defined herein.

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A "N-thiocarbamyl" group refers to a $R^xOC(=S)NR^y$- group with R^x and R^y as defined herein.

An "amino" group refers to an $-NH_2$ group.

A "C-amido" group refers to a $-C(=O)NR^xR^y$ group with R^x and R^y as defined herein.

A "C-thioamido" group refers to a $-C(=S)NR^xR^y$ group, with R^x and R^y as defined herein.

A "N-amido" group refers to a $R^xC(=O)NR^y$- group, with R^x and R^y as defined herein.

An "ureido" group refers to a $-NR^xC(=O)NR^yR^{y2}$ group with R^x and R^y as defined herein and R^{y2} defined the same as R^x and R^y.

A "guanidino" group refers to a $-R^xNC(=N)NR^yR^{y2}$ group, with R^x, R^y and R^{y2} as defined herein.

A "guanyl" group refers to a $R^xR^yNC(=N)$- group, with R^x and R^Y as defined herein.

A "cyano" group refers to a $-CN$ group.

A "silyl" group refers to a $-Si(R")_3$, with $R"$ as defined herein.

A "phosphonyl" group refers to a $P(=O)(OR^x)_2$ with R^x as defined herein.

A "hydrazino" group refers to a $-NR^xNR^yR^{y2}$ group with R^x, R^y and R^{y2} as defined herein.

The term "spiro" as used herein refers to ring systems in which there is one carbon atom common to two rings. Examples of "spiro" ring systems include, but are not limited to, spiropentane and spirohexane, shown below.

29
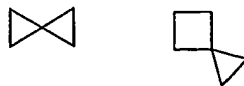
The term "fused" as used herein refers to ring systems in which two adjacent atoms are common to two rings. Examples of "fused" ring systems include, but are not limited to, decalin and indole, shown below.

5
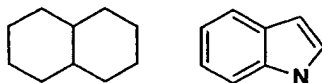
The term "bridged" as used herein refers to ring systems in which two non adjacent atoms are common to two or more rings. Examples of "bridged" ring systems include, but are not limited to, quinuclidine and

10   norbornane, shown below.
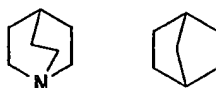
Any two adjacent R groups may combine to form an additional aryl, cycloalkyl, heteroary or heterolicyclic ring fused to the ring initially bearing

15   those R groups.

It is known in the art that nitogen atoms in heteroaryl systems can be "participating in a heteroaryl ring double bond", and this refers to the form of double bonds in the two tautomeric structures which comprise five-member

20   ring heteroaryl groups. This dictates whether nitrogens can be substituted as well understood by chemists in the art. The disclosure and claims of the present invention are based on the known general principles of chemical bonding. It is understood that the claims do not encompass structures known to be unstable or not able to exist based on the literature.

25

Physiologically acceptable salts and prodrugs of compounds disclosed herein are within the scope of this invention. The term "pharmaceutically acceptable salt" as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from

30   organic and inorganic acids such as, without limitation, hydrochloric acid,

hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfinic acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, and the like. The term "pharmaceutically acceptable salt" as used herein is also intended to

5   include salts of acidic groups, such as a carboxylate, with such counterions as ammonium, alkali metal salts, particularly sodium or potassium, alkaline earth metal salts, particularly calcium or magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (e.g.

10   hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or tris(hydroxymethyl)- aminomethane), or with bases such as piperidine or morpholine.

     In the method of the present invention, the term "antiviral effective

15   amount" means the total amount of each active component of the method that is sufficient to show a meaningful patient benefit, i.e., healing of acute conditions characterized by inhibition of the HIV infection. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to

20   combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The terms "treat, treating, treatment" as used herein and in the claims means preventing or ameliorating diseases associated with HIV infection.

25   The present invention is also directed to combinations of the compounds with one or more agents useful in the treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators,

30   antiinfectives, or vaccines, such as those in the following table.

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ANTIVIRALS

	Drug Name	Manufacturer	Indication
5	097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse trans-criptase (RT) inhibitor)
10			
	Amprenivir 141 W94 GW 141	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
15	Abacavir (1592U89) GW 1592	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
20	Acemannan	Carrington Labs (Irving, TX)	ARC
	Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
25			
	AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
30	AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
	Adefovir dipivoxil	Gilead Sciences	HIV infection
35	AL-721	Ethigen (Los Angeles, CA)	ARC, PGL HIV positive, AIDS
	Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
40			
	Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
45			

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5	Antibody which Neutralizes pH Labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
	AR177	Aronex Pharm	HIV infection, AIDS, ARC
10	Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
15	BMS-232623 (CGP-73547)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
	BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
20	CI-1012	Warner-Lambert	HIV-1 infection
	Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
25	Curdlan sulfate	AJI Pharma USA	HIV infection
	Cytomegalovirus Immune globin	MedImmune	CMV retinitis
30	Cytovene Ganciclovir	Syntex	Sight threatening CMV peripheral CMV retinitis
35	Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
40	Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
45	ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
	ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T

	DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
5 10	Efavirenz (DMP 266) (-)6-Chloro-4-(S)- cyclopropylethynyl- 4(S)-trifluoro- methyl-1,4-dihydro- 2H-3,1-benzoxazin- 2-one, STOCRINE	DuPont Merck	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
15	EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
	Famciclovir	Smith Kline	herpes zoster, herpes simplex
20	FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
25	GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
30 35	HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
	Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
40	Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
	Interferon alfa-n3	Interferon Sciences	ARC, AIDS
45	Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
50	ISIS 2922	ISIS Pharmaceuticals	CMV retinitis

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KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (RT inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)

Stavudine; d4T Didehydrodeoxy-thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	Genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies

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IMMUNOMODULATORS

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Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst	AIDS .
Bropirimine Acemannan	Pharmacia Upjohn Carrington Labs, Inc. (Irving, TX)	Advanced AIDS AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)

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Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma

	Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
5	Remune	Immune Response Corp.	Immunotherapeutic
10	rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
	rCD4-IgG hybrids		AIDS, ARC
15	Recombinant Soluble Human CD4	Biogen	AIDS, ARC
20	Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
	SK&F106528 Soluble T4	Smith Kline	HIV infection
25	Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
30	Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

35	Drug Name	Manufacturer	Indication
	Clindamycin with Primaquine	Pharmacia Upjohn	PCP
40	Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
45	Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
	Ornidyl Eflornithine	Merrell Dow	PCP

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Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	Cryptosporidial diarrhea
Intraconazole-R51211	Janssen-Pharm.	Histoplasmosis; cryptococcal Meningitis
Trimetrexate	Warner-Lambert	PCP
Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia assoc. with AZT Therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	Treatment of Anorexia assoc. W/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption Related to AIDS

Additionally, the compounds of the invention herein may be used in combination with another class of agents for treating AIDS which are called HIV entry inhibitors. Examples of such HIV entry inhibitors are discussed in DRUGS OF THE FUTURE 1999, 24(12), pp. 1355-1362; CELL, Vol. 99, pp.

243-246, Oct. 29, 1999; and DRUG DISCOVERY TODAY, Vol. 5, No. 5, May 2000, pp. 183-194.

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives, HIV entry inhibitors or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments of a compound of the present invention and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4) zidovudine and lamivudine and 141W94 and 1592U89; (5) zidovudine and lamivudine.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

40

Abbreviations

The following abbreviations, most of which are conventional
abbreviations well known to those skilled in the art, are used throughout the
5   description of the invention and the examples. Some of the abbreviations
used are as follows:

h	=	hour(s)
rt	=	room temperature
mol	=	mole(s)
mmol	=	millimole(s)
g	=	gram(s)
mg	=	milligram(s)
mL or ml	=	milliliter(s)
µl	=	microliter(s)
TFA	=	Trifluoroacetic Acid
DCE	=	1,2-Dichloroethane
CH_2Cl_2	=	Dichloromethane
THF	=	Tetrahydofuran
DEPBT	=	3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
P-EDC	=	Polymer supported 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EDC	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
DMF	=	N,N-dimethylformamide
DMAP	=	4-dimethylaminopyridine
HOBT	=	1-hydroxybenzotriazole
TOSMIC	=	tosylmethylisocyanide
Cbz	=	carbobenzyloxy
TPAP	=	tetrapropylammonium perruthenate
NMO	=	4-methylmorpholine N-oxide
TMEDA	=	N,N,N,N'-tetramethyl ethylenediamine
NMM	=	4-methylmorpholine
MeOH	=	methanol
EtOH	=	ethanol
EtOAc	=	ethyl acetate

Chemistry

The synthesis procedures and anti-HIV-1 activities of indoleoxoacetic piperazine analogs are summarized below. Procedures for making

5   intermediates and compounds of Formula I are shown in Schemes 1-41.

It should be noted that in many cases reactions are depicted for only one position of an intermediate, such as the R^5 position, for example. It is to be understood that such reactions could be used at other positions, such as

10   R^2-R^4, of the various intermediates. Reaction conditions and methods given in the specific examples are broadly applicable to compounds with other substitution and other tranformations in this application. Schemes 1 and 2 describe general reaction schemes for taking appropriately substituted indoles and converting them to compounds of Formula I. While these

15   schemes are very general, other permutations such as carrying a precursor or precursors to substituents R^2 through R^5 through the reaction scheme and then converting it to a compound of Formula I in the last step are also contemplated methods of this invention. Nonlimiting examples of such strategies follow in subsequent schemes.

20

Scheme 1
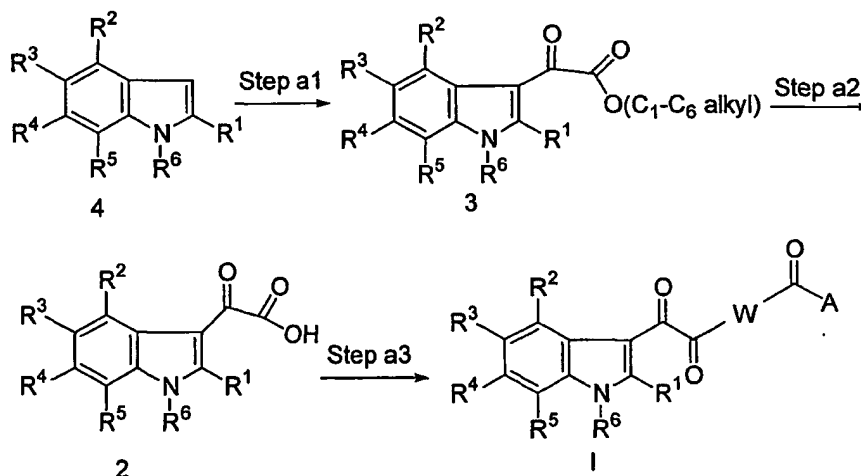
Starting indole intermediates of formula 4 (Scheme 1) are known or are readily prepared according to literature procedures, such as those

25   described in Gribble, G. (Refs. 24 and 99), Bartoli et al (Ref. 36), reference 37, or the book by Richard A. Sundberg in reference 40. Other methods for the preparation of indole intermediates include: the Leimgruber-Batcho

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Indole synthesis (reference 93); the Fisher Indole synthesis (references 94 and 95); the 2,3-rearrangement protocol developed by Gassman (reference 96); the annelation of pyrroles (reference 97); tin mediated cyclizations (reference 98); and the Larock palladium mediated cyclization of 2-alkynyl

5 . anilines. Many other methods of indole synthesis are known and a chemist with typical skill in the art can readily locate conditions for preparation of indoles which can be utilized to prepare compounds of Formula I.

Intermediates of Formula 3 are prepared by attachment of an oxalyl
10 ester moiety at the 3-position of the Formula 4 intermediate as described in Step a1 of Scheme 1. This transformation can be carried out by sequentially treating the Formula 4 intermediate with an alkyl Grignard reagent, followed by a zinc halide and then an oxalic acid mono ester in an aprotic solvent. Typical Grignard reagents used include methyl magnesium bromide and
15 ethyl magnesium bromide. The zinc halide is selected from zinc bromide or zinc chloride. Oxalic acid esters such as methyl oxalate or ethyl oxalate are used and aprotic solvents such as CH_2Cl_2, Et_2O, benzene, toluene, DCE, or the like may be used alone or in combination for this sequence. A preferred sequence is to treat intermediate 4 with 1) methylmagnesium bromide, 2)
20 zinc bromide, 3) methyl oxalate, to provide intermediate 3.

An alternative method for carrying out step 1a is acylation of the Formula 4 intermediate with ethyl oxalyl chloride in the presence of aluminum chloride in an inert solvent such as dichloromethane to provide the Formula 3
25 intermediate. Other alkyl mono esters of oxalic acid could also suffice for either method shown above. As listed in reference 104, Lewis acids other than aluminum chloride and solvents other than dichloromethane might also be used for the transformation in step a1.

30 The hydrolysis of the ester intermediate of Formula 3 to form the 3-indole oxoacetic acid of Formula 2 is shown in step a2 of Scheme 1. The usual conditions employ methanolic or ethanolic sodium hydroxide followed by acidification with aqueous hydrochloric acid of varying molarity but 1M HCl is preferred. Lithium hydroxide or potassium hydroxide could also be
35 employed and varying amounts of water could be added to the alcohols. Propanols or butanols could also be used as solvents. Elevated temperatures up to the boiling points of the solvents may be utilized if ambient temperatures do not suffice. Alternatively, the hydrolysis may be

43

carried out in a non polar solvent such as CH_2Cl_2 or THF in the presence of Triton B. Temperatures of −70 °C to the boiling point of the solvent may be employed but -10 °C is preferred. Other conditions for ester hydrolysis are listed in reference 58 and both this reference and many of the conditions for

5   ester hydrolysis are well known to chemists of average skill in the art. As shown in Scheme 2, step a4, oxalyl chloride can be used to install the oxoacetyl chloride group at the indole 3 position of intermediate 4 to provide the intermediate of Formula 5. Typically, inert solvents such as CH_2Cl_2 or DCE are used as solvents but THF and diethyl ether will also work. Step a4

10   might also be performed in the presence of a catalyst. The catalyst most preferred is aluminum chloride. Tin tetrachloride or titanium IV chloride might also be utilized in some applications. The chloride intermediate of Formula 5 can be coupled to an amine H-W-C(O)A in an inert solvent (e.g. CH_2Cl_2) in the presence of a tertiary amine (e.g. N,N-diisopropylethylamine) or pyridine

15   to gives compounds of Formula I (Step a5). The chloride could also be directly reacted with a low molecular weight alcohol such as MeOH to provide the an ester (intermediate of Formula 3, as shown in Scheme 1). The entire reaction sequence shown in Scheme 2, including reaction with oxalyl chloride and coupling to an alcohol or H-W-C(O)A could be carried out in a solvent

20   such as pyridine in the case of some indole intermediates of Formula 4. The amide coupling with amine H-W-C(O)A is shown in Scheme 1, step a3. The group W as referred to herein is eit
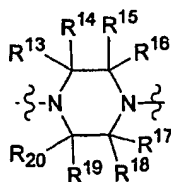
25

       One preferred method for carrying out this reaction is the use of the peptide coupling reagent 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT) and an amine H-W-C(O)A in DMF solvent containing a tertiary amine such as N,N-diisopropylethylamine. Commonly used amide

30   bond coupling conditions, e.g. EDC with HOBT or DMAP, are also employed in some examples. Typical stoichiometries are given in the specific examples but these ratios may be modified.

44

The amide bond construction reactions depicted in step a3 or step a5 of Schemes 1 and 2 respectively could be carried out using the specialized conditions described herein or alternatively by applying the conditions or coupling reagents for amide bond construction described for steps a16-a18

5   of this application. Some specific nonlimiting examples are given in this application.

Additional procedures for synthesizing, modifying and attaching groups : $(C=O)_m$-WC(O)-A are contained in PCT WO 00/76521.

10
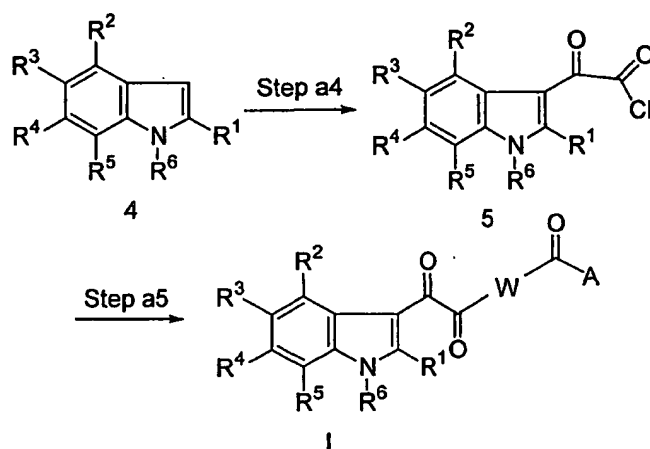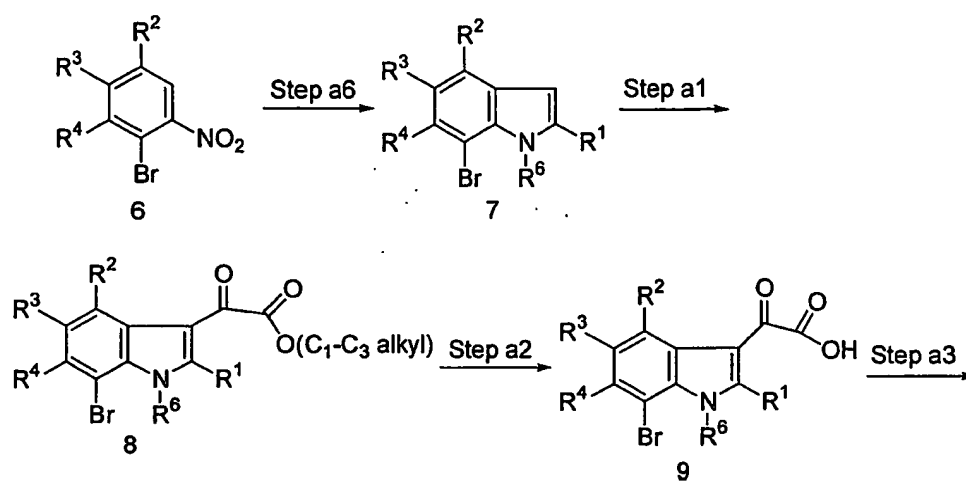
Scheme 2

Scheme 3

Scheme 4
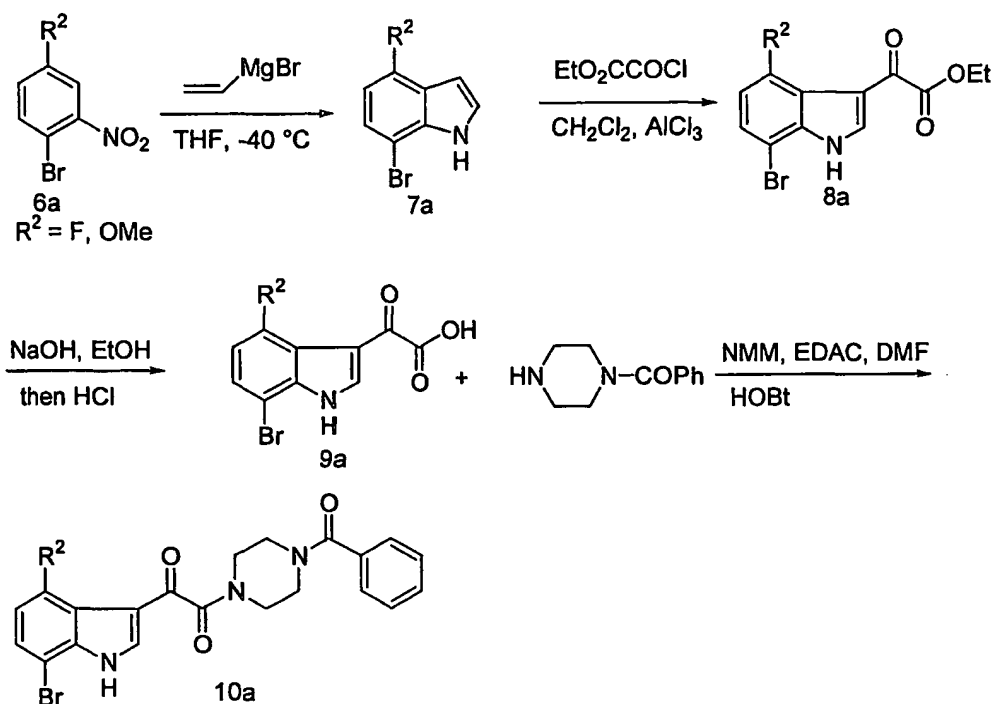
Scheme 4 shows the preparation of an indole intermediate 7a, acylation of 7a with ethyl oxalyl chloride to provide intermediate 8a, followed by ester hydrolysis to provide intermediate 9a, and amide formation to provide intermediate 10a.

Alternatively, the acylation of an indole intermediate, such as 7a', could be carried out directly with oxalyl chloride followed by base mediated piperazine coupling to provide an intermediate of Formula 10a' as shown in Scheme 5.

Scheme 5
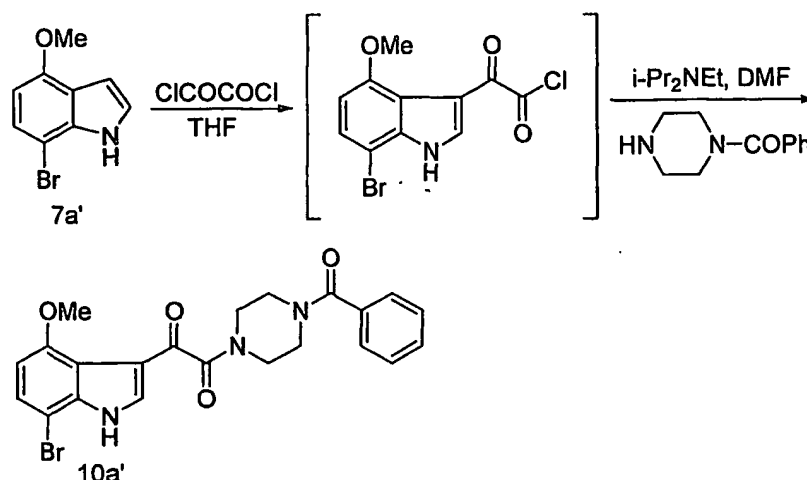
Scheme 6 depicts the preparation of a key aldehyde intermediate, **14**, using a procedure adapted from reference 90 which are the methods of

5   Gilmore et.al. The aldehyde substituent is shown only at the R^5 position for the sake of clarity, and should not be considered as a limitation of the methodology as the aldehyde functionality could be introduced at any of positions R^1-R^5. In Scheme 6, step a7, a bromide intermediate, **7**, is converted into an aldehyde intermediate, **11**, by metal-halogen exchange

10   and subsequent reaction with dimethylformamide in an appropriate aprotic solvent. Typical bases used include, but are not limited to, alkyl lithium bases such as n-butyl lithium, sec butyl lithium or tert butyl lithium or a metal such as lithium metal. A preferred aprotic solvent is THF. Typically the transmetallation with n butyl lithium is initiated at -78 °C. The reaction may

15   be allowed to warm to allow the transmetalation to go to completion depending on the reactivity of the bromide intermediate, **7**. The reaction is then recooled to −78 °C and allowed to react with N, N-dimethylformamide. (allowing the reaction to warm may be required to enable complete reaction) to provide intermediate **11**. Intermediate **11** was then further elaborated to

20   intermediates **12**, **13** and **14** as shown in Scheme 6 (steps a1, a2, a3) according to the method described in Scheme 1. The amide coupling step utilized 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT) as the preferred method.

48

Other methods for introduction of an aldehyde group to form intermediates of formula 11 include transition metal catalyzed carbonylation reactions of suitable bromo, trifluoromethane sulfonates(yl), or stannanes(yl) indoles. Alternative the aldehydes can be introduced by reacting indolyl

5   anions or indolyl Grignard reagents with formaldehyde and then oxidizing with MnO_2 or TPAP/NMO or other suitable oxidants to provide intermediate 11.

References 38 and 39 provide methods for preparing indoles with

10   substituents at the 7-position (i.e. position to which R^5 is attached). These references provide methods for functionalizing the C-7 position of indoles by either 1) protecting the indole nitrogen with 2,2-diethyl propanoyl group and then deprotonating the 7-position with sec/BuLi in TMEDA to give an anion. This anion may be quenched with DMF, formaldehyde, or carbon dioxide to

15   give the aldehyde, benzyl alcohol, or carboxylic acid respectively. Similar tranformations can be achieved by converting indoles to indoline, lithiation at C-7 and then reoxidation to the indole. The oxidation level of any of these products may be adjusted by methods well known in the art as the interconversion of alcohol, aldehyde, and acid groups has been well studied.

20   It is also well understood that a protected alcohol, aldehyde, or acid group could be present in the starting indole and carried through the synthetic steps to a compound of Formula I in a protected form until they can be converted into the desired substituent at the R^1 through R^5 position. For example, a hydroxymethyl group can be protected as a benzyl ether or silyl ether or

25   other alcohol protecting group; an aldehyde may be carried as an acetal, and an acid may be protected as an ester or ortho ester until deprotection is desired and carried out by literature methods.

Scheme 6
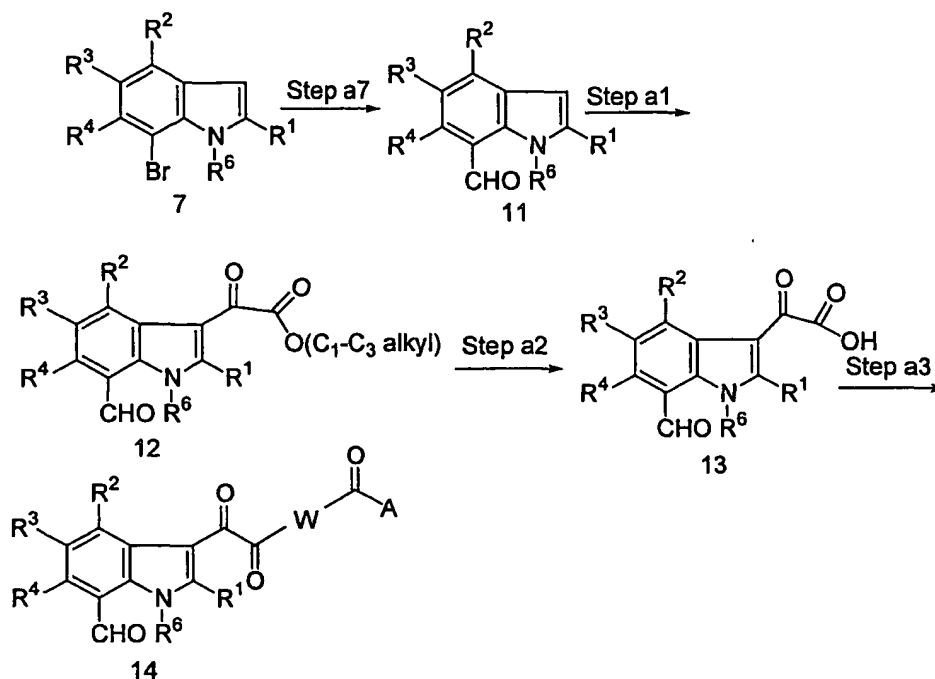
Scheme 7 provides a more specific example of the method of Gilmore
for preparation of an important aldehyde intermediate, 14a. Bromo indole
5   intermediate, 7a, is treated with n-butyl lithium followed by N, N-
dimethylformamide in THF at –78 °C to provide the aldehyde intermediate,
11a. Intermediate 11a is then acylated with ethyl oxalyl chloride to provide
intermediate 12a which is hydrolyzed to give intermediate 13a. Intermediate
13a is subjected to amide formation as shown to provide intermediate 14a.
10

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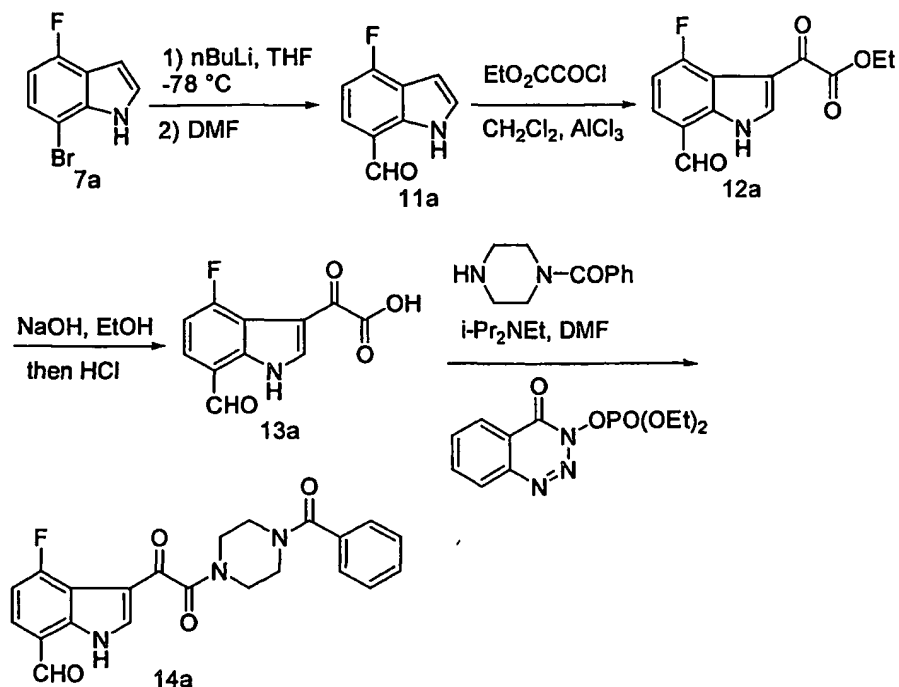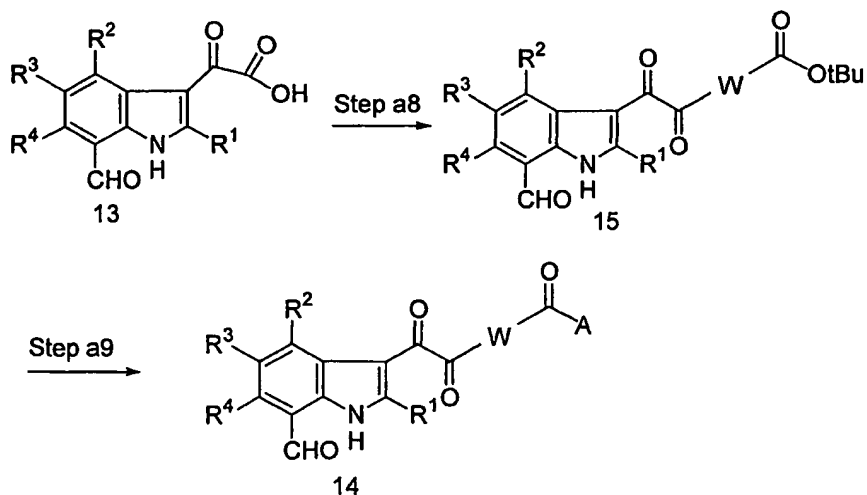
Scheme 7

Scheme 8

5   Scheme 8 depicts a general method for modifying the substituent A.
Coupling of H-W-C(O)OtBu using the conditions described previously for W
in Scheme 1 provides Boc protected intermediate, 15. Intermediate 15 is
then deprotected by treatment with an acid such as TFA, hydrochloric acid or
formic acid using standard solvents such as CH$_2$Cl$_2$ or dioxane and

temperatures between –78 °C and 100 °C. Other acids such as aqueous
hydrochloric or perchloric may also be used for deprotection. Alternatively
other nitrogen protecting groups on W such as Cbz or TROC, may be utilized
and could be removed via hydrogenation or treatment with zinc respectively.

5   A stable silyl protecting group such as phenyl dimethylsilyl could also be
employed as a nitrogen protecting group on W and can be removed with
fluoride sources such as tetrabutylammonium fluoride. The group A(C=O)- is
then attached by using the corresponding carboxylic acid, A(C=O)OH, the
acid chloride, A(C=O)Cl, or other activated acid derivative. Coupling

10   methods as described for attaching the piperazine to the oxalic acid (above),
for the formation of the monosubstituted piperazines (below), or for the
preparation of amides at R^1-R^5 (below), may be utilized.

         Scheme 9 provides a method for the preparation of indole

15   intermediates bearing a carboxylic acid group, such as intermediate 20. As
shown in the Scheme 9, step a10, one method for forming the nitrile
intermediate, 16, is by cyanide displacement of the bromide at the C-7
position (the R^5 position) of the requisite indole intermediate, 7. The
cyanide reagent used can be sodium cyanide, or more preferably copper or

20   zinc cyanide. The reactions may be carried out in numerous solvents which
are well known in the art. For example DMF is used in the case of copper
cyanide. The conversion of the cyano intermediate, 16, to the carboxylic acid
intermediate, 17, is depicted in step a11. Many methods for the conversion
of nitriles to acids are well known in the art and may be employed. Suitable

25   conditions for the conversion of intermediate 16 to intermediate 17 employ
potassium hydroxide, water, and an aqueous alcohol such as ethanol.
Typically the reaction must be heated at refluxing temperatures for one to
100h. The acid intermediate, 17, may then be esterified to give intermediate
18. Intermediate 16 can also be converted directly to intermediate 18 by

30   treating a solution of intermediate 16 in an alcohol (typically methanol)
saturated with hydrogen chloride. Typically, refluxing temperature is required
for the transformation. Intermediate 18 may then be converted to
intermediate 19 according to the procedure described in Scheme 2.
Intermediate 19 may then be hydrolyzed to provide intermediate 20.

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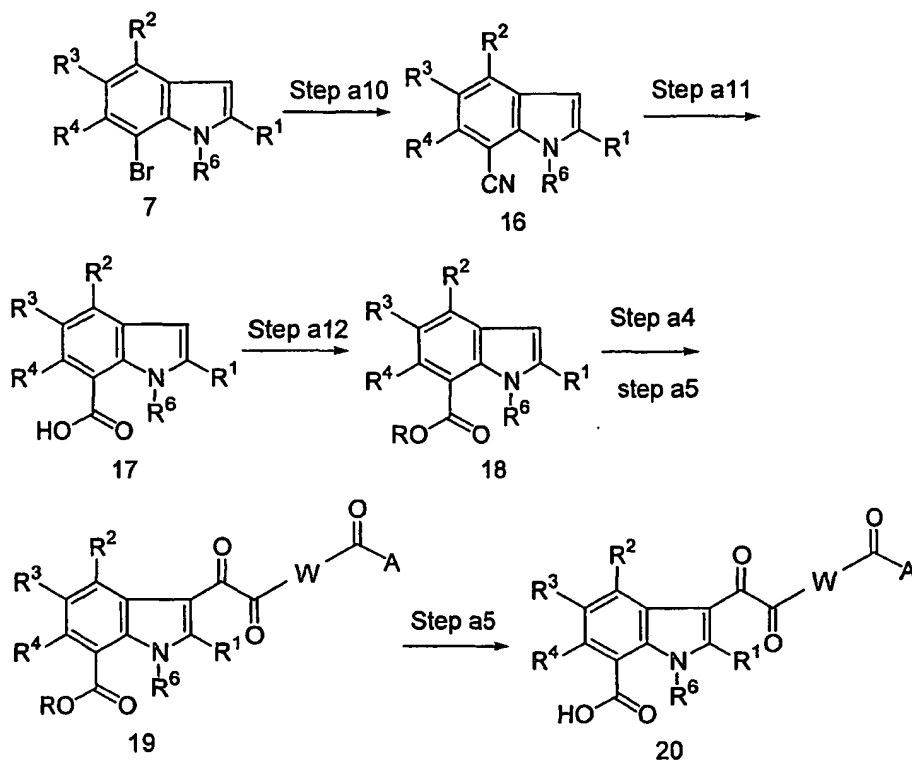
Scheme 9

As shown in Scheme 10, step a13, another preparation of the indoleoxoacetylpiperazine 7-carboxylic acids, 20, is carried out by oxidation of the corresponding 7-carboxaldehyde, 14. The preparation of the aldehyde intermediate, 14, has been described previously in this application. Numerous oxidants are suitable for the conversion of aldehyde to acid and many of these are described in standard organic chemistry texts such as: Larock, Richard C., Comprehensive organic transformations : a guide to functional group preparations 2nd ed. New York : Wiley-VCH, 1999. One preferred method is the use of silver nitrate or silver oxide in a solvent such as aqueous or anhydrous MeOH at a temperature of ~25 °C or as high as reflux. The reaction is typically carried out for one to 48 h and is typically monitored by TLC or LC/MS until complete conversion of product to starting material has occurred. Alternatively, $KMnO_4$ or CrO_3/H_2SO_4 could be utilized (see ref. 91).

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Scheme 10
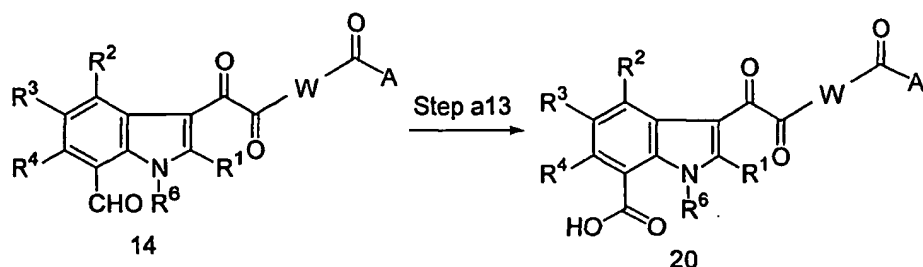
Scheme 11 gives a specific example of the oxidation of an aldehyde intermediate, 14a, to provide the carboxylic acid intermediate, 20a.

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Scheme 11
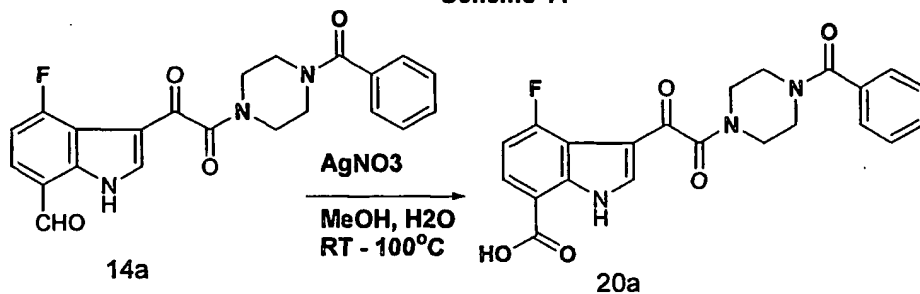
Alternatively, intermediate 20 can be prepared by the nitrile method of synthesis carried out in an alternative order as shown in Scheme 12. The
10   nitrile hydrolysis step can be delayed and the nitrile carried through the synthesis to provide a nitrile 22, which could be hydrolyzed to provide the free acid, 20, as above. As described for the conversion of intermediate 16 to intermediate 18, nitrile 22 could also be converted to an ester of acid 20 under similar conditions.

15

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Scheme 12
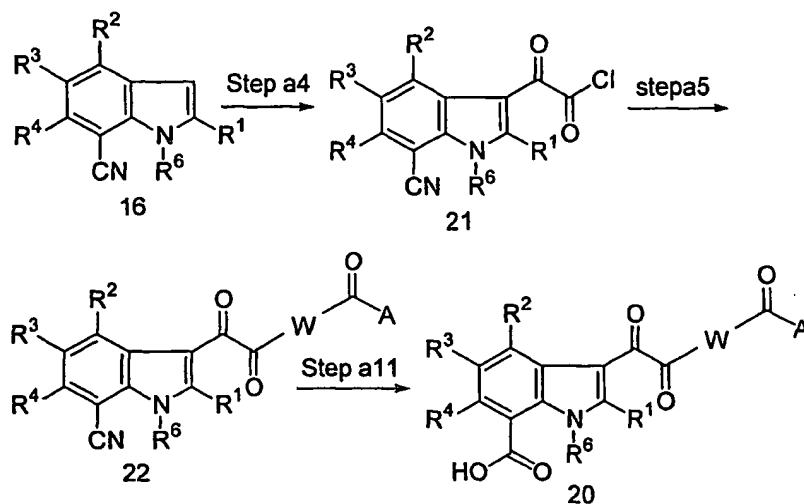
It is well known in the art that heterocycles may be prepared from an aldehyde, carboxylic acid, carboxylic acid ester, carboxylic acid amide,
5   carboxylic acid halide, or cyano moiety or attached to another carbon substituted by a bromide or other leaving group such as a triflate, mesylate, chloride, iodide, or phosponate. The methods for preparing such intermediates from intermediates typified by the carboxylic acid intermediate, 20, bromo intermediate, 10, or aldehyde intermediate, 14 described above
10   are known by a typical chemist practitioner. The methods or types of heterocycles which may be constructed are described in the chemical literature. Some representative references for finding such heterocycles and their construction are included in reference 77 through 89 but should in no way be construed as limiting. However, examination of these references
15   shows that many versatile methods are available for synthesizing diversely substituted heterocycles and it is apparent to one skilled in the art that these can be applied to prepare compounds of Formula I. Chemists well versed in the art can now easily, quickly, and routinely find numerous reactions for preparing heterocycles, amides, oximes or other substituents from the above
20   mentioned starting materials by searching for reactions or preparations using a conventional electronic database such as Scifinder (American Chemical Society), Crossfire (Beilstein), Theilheimer, or Reaccs (MDS). The reaction conditions identified by such a search can then be employed using the substrates described in this application to produce all of the compounds
25   envisioned and covered by this invention. In the case of amides, commercially available amines can be used in the synthesis. Alternatively,

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the above mentioned search programs can be used to locate literature
preparations of known amines or procedures to synthesize new amines.
These procedures are then carried out by one with typical skill in the art to
provide the compounds of Formula I for use as antiviral agents.

5

As shown below in Scheme 13, step a13, suitable substituted indoles,
such as the bromoindole intermediate, 10, may undergo metal mediated
couplings with aryl groups, heterocycles, or vinyl stannanes to provide
compounds within Formula I wherein R^5 is aryl, heteroaryl, or heteroalicyclic

10   for example. The bromoindole intermediates, 10 (or indole triflates or iodides)
may undergo Stille-type coupling with heteroarylstannanes as shown in
Scheme 13, step a14. Conditions for this reaction are well known in the art
and references 72-74 as well as reference 91 provide numerous conditions in
addition to the specific examples provided in Scheme 14 and in the specific

15   embodiments. It can be well recognized that an indole stannane could also
couple to a heterocyclic or aryl halide or triflate to construct compounds of
Formula I. Suzuki coupling (reference 71) between the bromo intermediate,
10, and a suitable boronate could also be employed and some specific
examples are contained in this application. Other Suzuki conditions,

20   partners, and leaving groups have utility. Suzuki couplings between chloro
intermediates are also feasible. If standard conditions fail new specialized
catalysts and conditions can be employed. Procedures describing catalysts
which are useful for coupling boronates with aryl and heteroaryl chlorides are
known in the art (reference 100 a-g). The boronate could also be formed on

25   the indole and then subjected to Suzuki coupling conditions.

Scheme 13
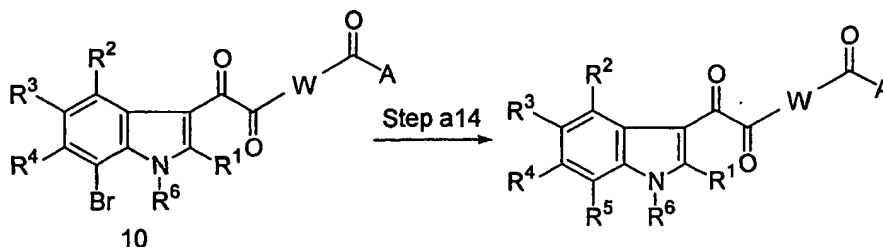
56

Scheme 14
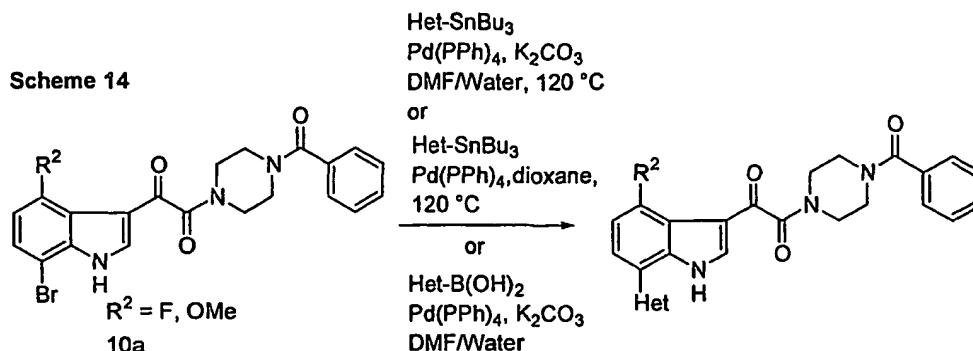
As shown in Scheme 15, step a15, aldehyde intermediates, 14, may
be used to generate numerous compounds within Formula I. The aldehyde
5   group may be a precursor for any of the substituents R^1 through R^5 but the
transformation for R^5 is depicted below for simplicity.

Scheme 15
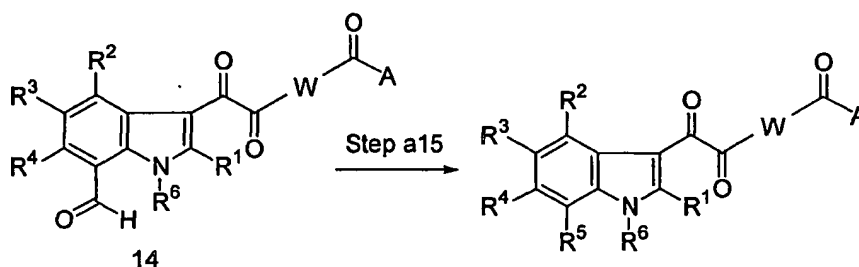
10   The aldehyde intermediate 14, may be reacted to become
incorporated into a ring as described in the claims or be converted into an
acyclic group. The aldehyde, 14, may be reacted with a Tosmic based
reagent to generate oxazoles (references 42 and 43 for example). The
aldehyde, 14, may be reacted with a Tosmic reagent and than an amine to
15   give imidazoles as in reference 55 or the aldehyde intermediate, 14, may be
reacted with hydroxylamine to give an oxime which is a compound of
Formula I as described below. Examples of imidazole synthesis are
contained within the experimental section. Oxidation of the oxime with NBS,
t-butyl hypochlorite, or the other known reagents would provide the N-oxide
20   which react with alkynes or 3 alkoxy vinyl esters to give isoxazoles of varying
substitution. Reaction of the aldehyde intermediate 14, with the known
reagent, 23 (reference 70) shown below under basic conditions would
provide 4-aminotrityl oxazoles.

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23
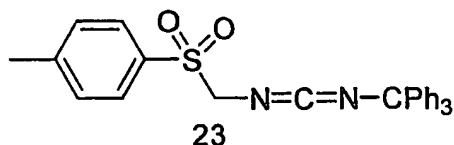
Removal of the trityl group under standard acidic conditions (TFA, anisole for example) would provide 4-amino oxazoles which could be substituted by

5   acylation, reductive alkylation or alkylation reactions or heterocycle forming reactions. The trityl could be replaced with an alternate protecting group such as a monomethoxy trityl, Cbz, benzyl, or appropriate silyl group if desired. Reference 76 demonstrates the preparation of oxazoles containing a triflouoromethyl moiety and the conditions described therein demonstrates

10 the synthesis of oxazoles with fluorinated methyl groups appended to them.

The aldehyde could also be reacted with a metal or Grignard (alkyl, aryl, or heteroaryl) to generate secondary alcohols. These would be efficacious or could be oxidized to the ketone with TPAP or MnO_2 or PCC for

15 example to provide ketones of Formula I which could be utilized for treatment or reacted with metal reagents to give tertiary alcohols or alternatively converted to oximes by reaction with hydroxylamine hydrochlorides in ethanolic solvents. Alternatively, the aldehyde could be converted to benzyl amines via reductive amination. An example of oxazole formation via a

20 Tosmic reagent is shown below in Scheme 16.

Scheme 16
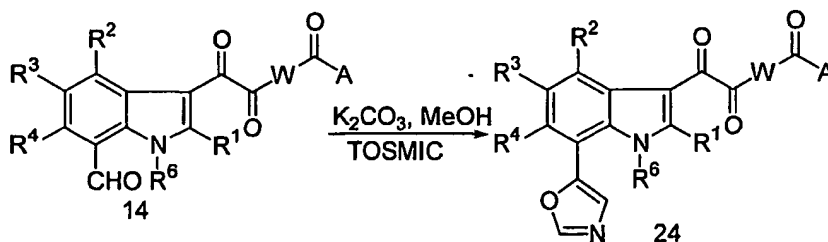
As can be seen from Scheme 17 in step a16, a cyano intermediate,

25 such as 22, may be directly converted to compounds within Formula I via heterocycle formation or reaction with organometallic reagents.

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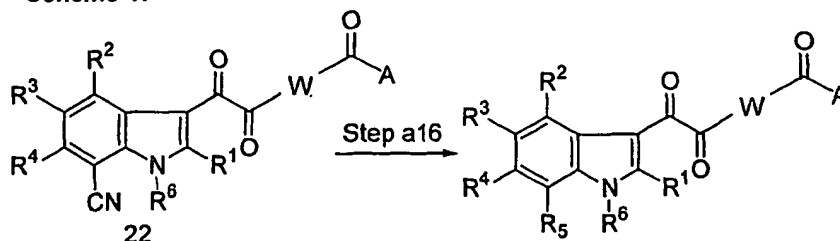
Scheme 17

Scheme 18 shows acylation of a cyanoindole intermediate of formula
16 with oxalyl chloride to give acid chloride, 21, which was coupled with the
appropriate benzoylpiperazine or pyridinylcarbonylpiperazine derivative in the
presence of base to provide 25.

Scheme 18
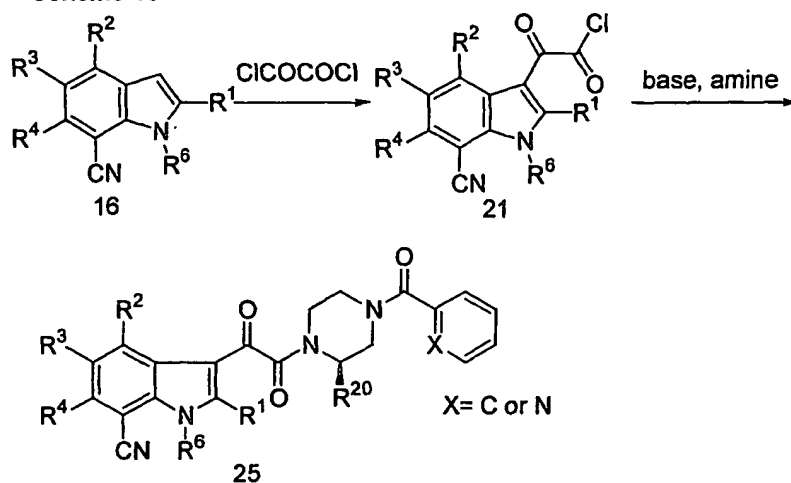
The nitrile intermediate, 25, was converted to the tetrazole of formula
26, which was alkylated with trimethylsilyldiazomethane to give the
compound of formula 27 (Scheme 19).

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Scheme 19

X = C or N

TMS-CHN₂
MeOH / PhH
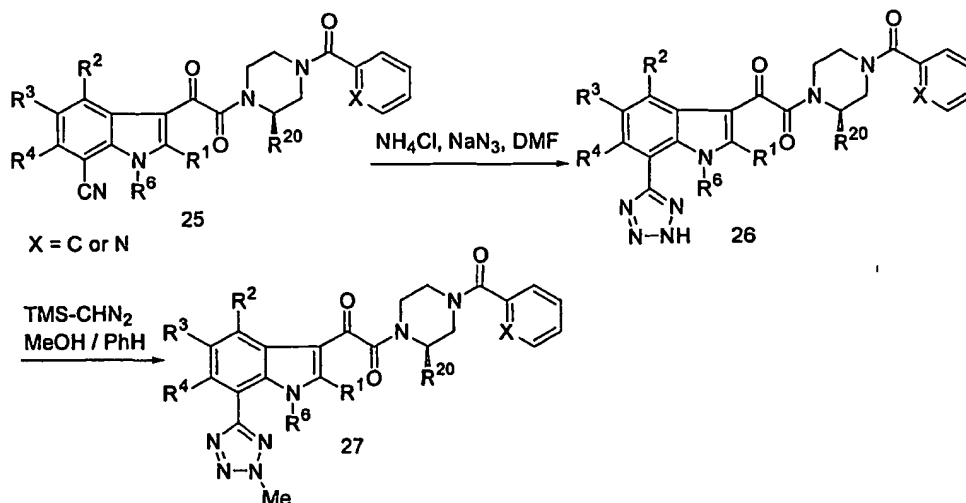
Tetrazole alkylation with alkyl halides (R-X, Scheme 20) required
alkylation prior to indole acylation as shown in Scheme 20 but indole
5   acylation prior to alkylation is useful in certain other circumstances.
Intermediate 16 was converted to tetrazole, 28, which was alkylated to
provide 29. Intermediate 29 was then acylated and hydrolyzed to provide 30
which was subjected to amide formation to provide 31. The group appended
to the tetrazole may be quite diverse in both size and structure and this
10   substitution has been found to modulate the properties of compounds of
Formula I.

Scheme 20
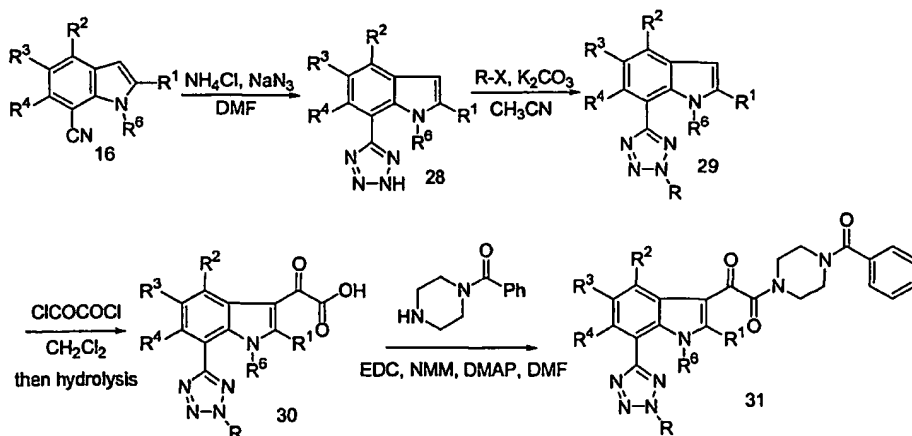
15   Scheme 21, eq.1, shows the oxadiazolone, 34a, was prepared by the
addition of hydroxylamine to the nitrile, 32, followed by ring closure of

60

intermediate 33 with phosgene. Alkylation of oxadiazolone, 34a, with trimethylsilyldiazomethane gave the compound of formula 35a.

Scheme 21

(eq. 1)

(eq. 2)

(eq. 3)
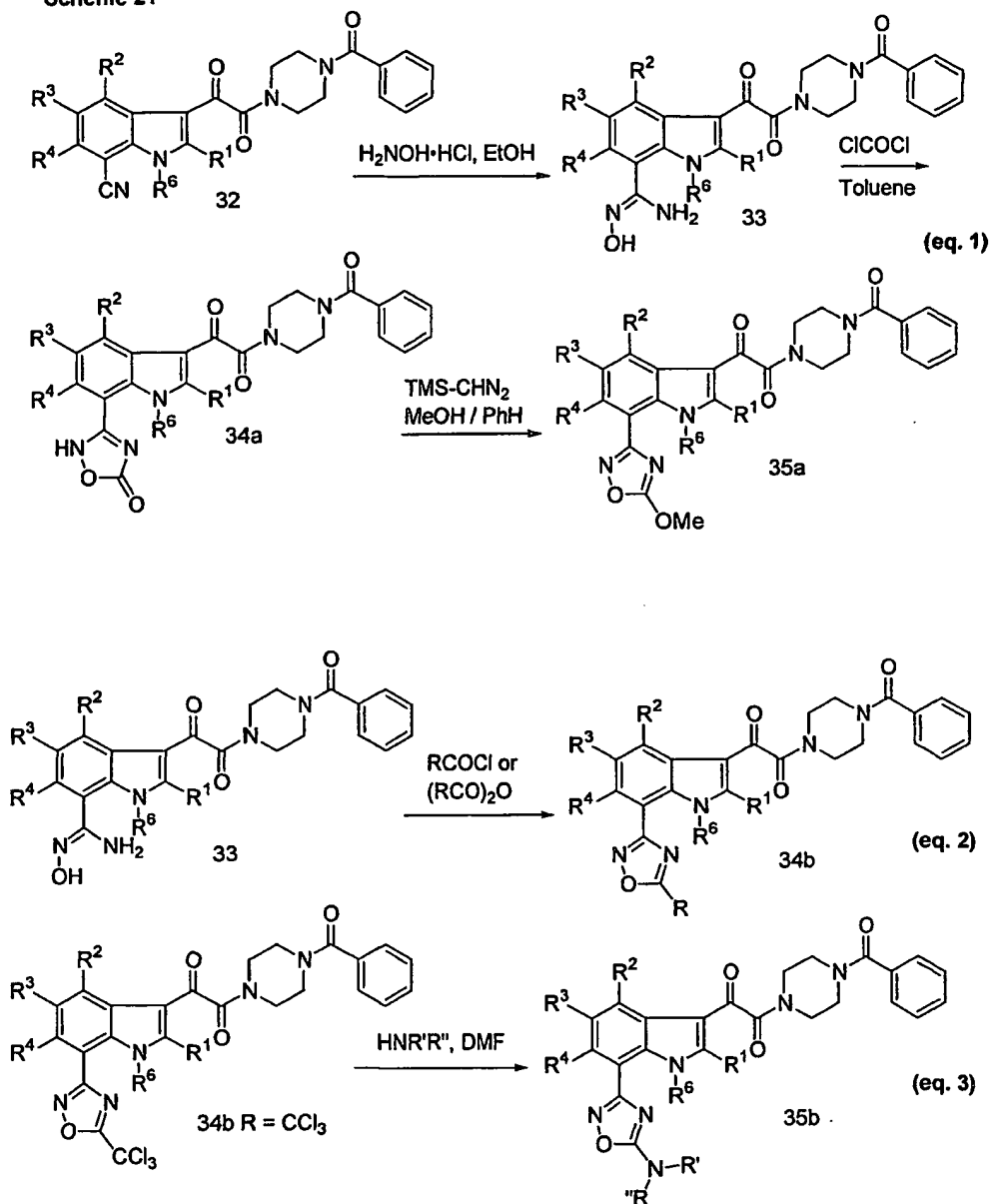
Cyclization of intermediate 33 with orthoformate (e.g. trimethylorthoformate or triethylorthoformate) will give oxadiazole. An example of such chemistry is provided in Example 79 of the experimental section. Cyclization of intermediate 33 to 5-subastituted oxadiazoles of Formula 34b can be performed using acid chlorides or anhydrides (eq. 2). These cyclization

61

reactions require the use of elevated temperature, and with or without an added base (tertiary alkylamine e.g. N,N-disopropylethylamine, or pyridine). When R = CCl_3 in Formula 34b, the trichloromethyl oxadiazole intermediate can undergo nucleophilic substitution (Reference 109) in a polar solvent (e.g.

5   DMF). Primary and secondary amine nucleophiles (R' and R" can represent hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl etc.) are prefered in these reactions to provide aminooxadiazole of Formula 35b (eq.3).

The 7-cyanoindole, 32, can also be efficiently converted to the imidate

10   ester under conventional Pinner conditions using 1,4-dioxane as the solvent. The imidate ester can be reacted with nitrogen, oxygen and sulfur nucleophiles to provide C7-substituted indoles, for example: imidazolines, benzimidazoles, azabenzimidazoles, oxazolines, oxadiazoles, thiazolines, triazoles, pyrimidines and amidines etc. (reference 101). An example of such

15   chemistry used to prepare triazoles is shown in Example 78, Example 111 and Example 127 to 131 of the experimental section.

Scheme 22 shows addition of either hydroxylamine or hydroxylamine acetic acid to aldehyde intermediate 36 gave oximes of Formula 37.

20
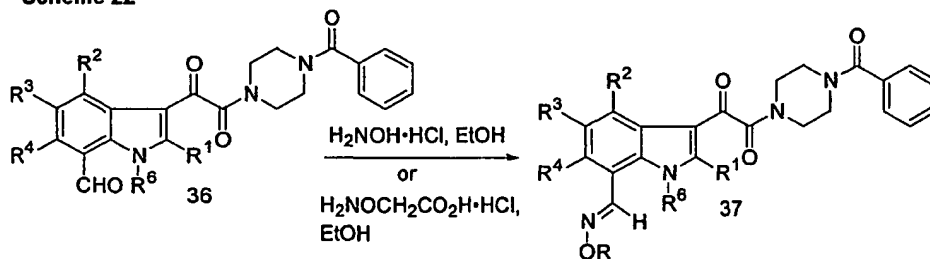
Scheme 22

An acid may be a precursor for substituents R^1 through R^5 when it occupies the corresponding position such as R^5 as shown in Scheme 23.

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Scheme 23
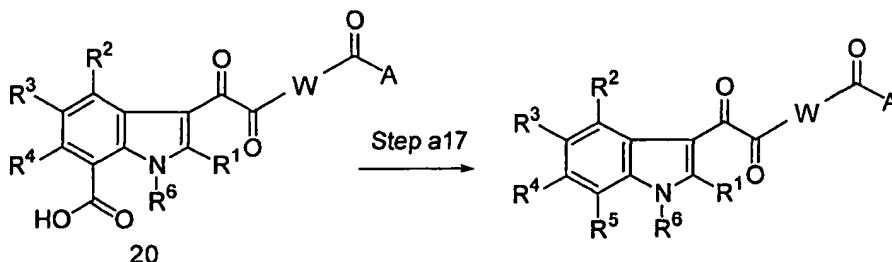
An acid intermediate, such as 20, may be used as a versatile precursor to generate numerous substituted compounds. The acid could be converted to hydrazonyl bromide and then a pyrazole via reference 53. Methodology for pyrazole synthesis is contained in the experimental section.

5   One method for general heterocycle synthesis would be to convert the acid to an alpha bromo ketone (ref 75) by conversion to the acid chloride using standard methods, reaction with diazomethane, and finally reaction with HBr. The alpha bromo ketone could be used to prepare many different compounds of Formula I as it can be converted to many heterocycles or

10   other compounds of Formula I. Alpha amino ketones can be prepared by displacement of the bromide with amines. Alternatively, the alpha bromo ketone could be used to prepare heterocycles not available directly from the aldeheyde or acid. For example, using the conditions of Hulton in reference 41 to react with the alpha bromo ketone would provide oxazoles. Reaction of

15   the alpha bromoketone with urea via the methods of reference 44 would provide 2-amino oxazoles. The alpha bromoketone could also be used to generate furans using beta keto esters(ref 45-47) or other methods, pyrroles (from beta dicarbonyls as in ref 48 or by Hantsch methods (ref 49) thiazoles , isoxazoles and imidazoles (ref 56) example using literature procedures.

20   Coupling of the aforementioned acid chloride with N-methyl-O-methyl hydroxyl amine would provide a "Weinreb Amide" which could be used to react with alkyl lithiums or Grignard reagents to generate ketones. Reaction of the Weinreb amide with a dianion of a hydroxyl amine would generate isoxazoles (ref 51). Reaction with an acetylenic lithium or other carbanion

25   would generate alkynyl indole ketones. Reaction of this alkynyl intermediate with diazomethane or other diazo compounds would give pyrazoles (ref 54). Reaction with azide or hydroxyl amine would give heterocycles after elimination of water. Nitrile oxides would react with the alkynyl ketone to give isoxazoles (ref 52). Reaction of the initial acid to provide an acid chloride

30   using for example oxalyl chloride or thionyl chloride or triphenyl phosphine/ carbon tetrachloride provides a useful intermediate as noted above. Reaction of the acid chloride with an alpha ester substituted isocyanide and base would give 2-substituted oxazoles (ref 50). These could be converted to amines, alcohols, or halides using standard reductions or Hoffman/Curtius

35   type rearrangements.

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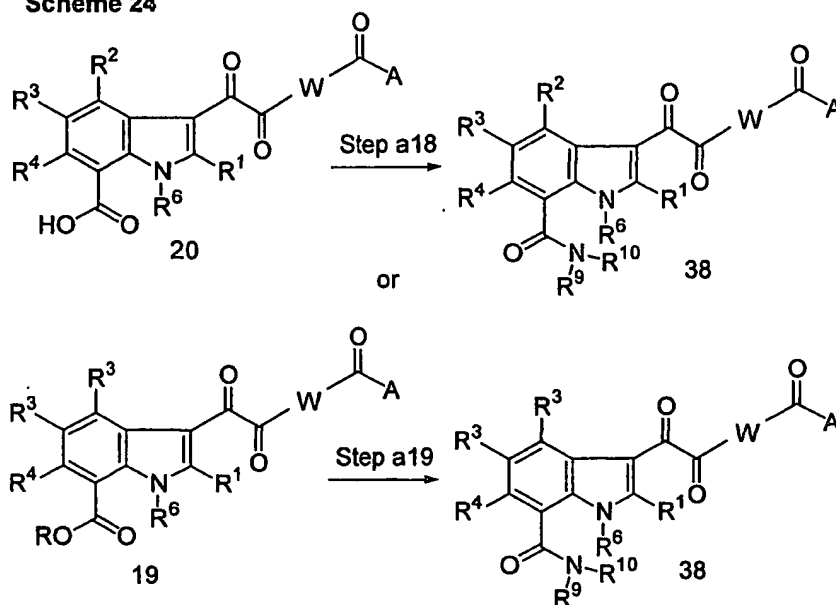
Scheme 24

Steps a17, a18, and a19 encompasses reactions and conditions for
1°, 2° and 3° amide bond formation as shown in Scheme 23 and 24 which
5   provide compounds such as those of Formula 38.

The reaction conditions for the formation of amide bond encompass
any reagents that generate a reactive intermediate for activation of the
carboxylic acid to amide formation, for example (but not limited to), acyl
10   halide, from carbodiimide, acyl iminium salt, symmetrical anhydrides, mixed
anhydrides (including phosphonic/phosphinic mixed anhydrides), active
esters (including silyl ester, methyl ester and thioester), acyl carbonate, acyl
azide, acyl sulfonate and acyloxy N-phosphonium salt. The reaction of the
indole carboxylic acids with amines to form amides may be mediated by
15   standard amide bond forming conditions described in the art. Some
examples for amide bond formation are listed in references 59-69 and 91,
and 92 but this list is not limiting. Some carboxylic acid to amine coupling
reagents which are applicable are EDC, Diisopropylcarbodiimide or other
carbodiimides, PyBop (benzotriazolyloxytris(dimethylamino) phosphonium
20   hexafluorophosphate), 2-(1H-benzotriazole-1-yl)-1, 1, 3, 3-tetramethyl
uronium hexafluorophosphate (HBTU). Some references for amide bond
formation are provided in references 59-69. A particularly useful method for
indole 7-carboxylic acid to amide reactions is the use of carbonyl imidazole
as the coupling reagent as described in reference 92. The temperature of

this reaction may be lower than in the cited reference , from 80 °C (or

possibly lower) to 150 °C or higher. A more specific application is depicted in

Scheme 25.

Scheme 25

1,1'carbonyldiimidazole
$\longrightarrow$
R^9NH_2, THF, reflux
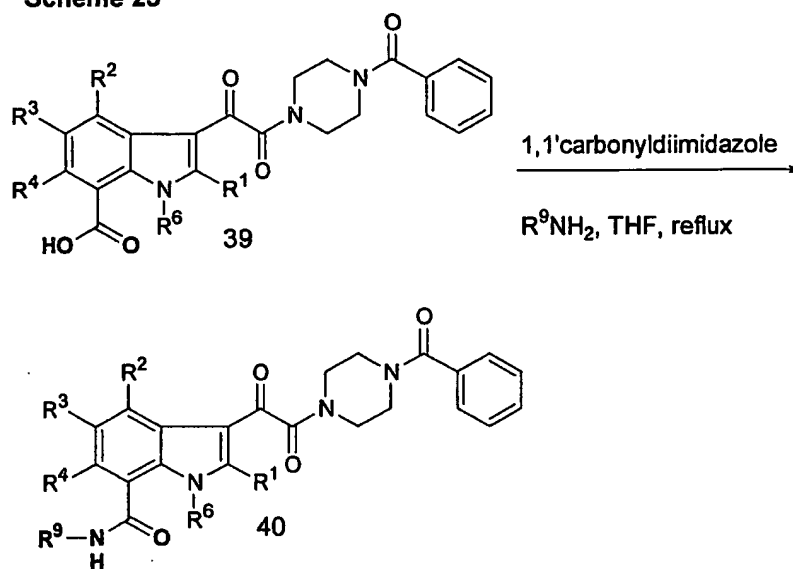
The following four general methods provide a more detailed
description for the preparation of indolecarboamides and these methods
were employed for the synthesis of compounds of Formula I.

Method 1:

To a mixture of an acid intermediate, such as 20, (1 equiv., 0.48
mmol), an appropriate amine (4 equiv.) and DMAP (58 mg, 0.47 mmol)
dissolved CH_2Cl_2 (1 mL) was added EDC (90 mg, 0.47 mmol). The resulting
mixture was shaken at rt for 12h, and then evaporated *in vacuo*. The residue
was dissolved in MeOH, and subjected to preparative reverse phase HPLC
purification.

Method 2:

To a mixture of an appropriate amine (4 equiv.) and HOBT (16 mg,
0.12 mmol) in THF (0.5 mL) was added an acid intermediate, such as 20, (25
mg, 0.06 mmol) and NMM (50 µl, 0.45 mmol), followed by EDC (23 mg, 0.12

mmol). The reaction mixture was shaken at rt for 12 h. The volatiles were evaporated *in vacuo*; and the residue dissolved in MeOH and subjected to preparative reverse phase HPLC purification.

5 Method 3:

To a mixture of an acid intermediate, such as 20, (0.047 mmol), amine (4 equiv.) and DEPBT (prepared according to Li, H.; Jiang, X. Ye, Y.; Fan, C.; Todd, R.; Goodman, M. *Organic Letters* **1999**, *1*, 91; 21 mg, 0.071 mmol)
10 in DMF (0.5 mL) was added TEA (0.03 mL, 0.22 mmol). The resulting mixture was shaken at rt for 12 h; and then diluted with MeOH (2 mL) and purified by preparative reverse phase HPLC.

Method 4:
15

A mixture of an acid intermediate, such as 20, (0.047mmol) and 8.5 mg (0.052mmol) of 1,1-carbonyldiimidazole in anhydrous THF (2 mL) was heated to reflux under nitrogen. After 2.5h, 0.052 mmol of amine was added and heating continued. After an additional period of 3~20 h at reflux, the
20 reaction mixture was cooled and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to provide compounds of Formula I or precursors of such compounds.

In addition, the carboxylic acid may be converted to an acid chloride
25 using reagents such as thionyl chloride (neat or in an inert solvent) or oxalyl chloride in a solvent such as benzene, toluene, THF, or CH_2Cl_2. The amides may alternatively, be formed by reaction of the acid chloride with an excess of ammonia, primary, or secondary amine in an inert solvent such as benzene, toluene, THF, or CH_2Cl_2 or with stoichiometric amounts of amines
30 in the presence of a tertiary amine such as triethylamine or a base such as pyridine or 2,6-lutidine. Alternatively, the acid chloride may be reacted with an amine under basic conditions (Usually sodium or potassium hydroxide) in solvent mixtures containing water and possibly a miscible co solvent such as dioxane or THF.   Scheme 25B depicts a typical preparation of an acid
35 chloride and derivatization to an amide of Formula I.   Additionally, the carboxylic acid may be converted to an ester preferably a methyl or ethyl ester and then reacted with an amine. The ester may be formed by reaction with diazomethane or alternatively trimethylsilyl diazomethane using

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standard conditions which are well known in the art. References and procedures for using these or other ester forming reactions can be found in reference 58 or 91.

Scheme 25A
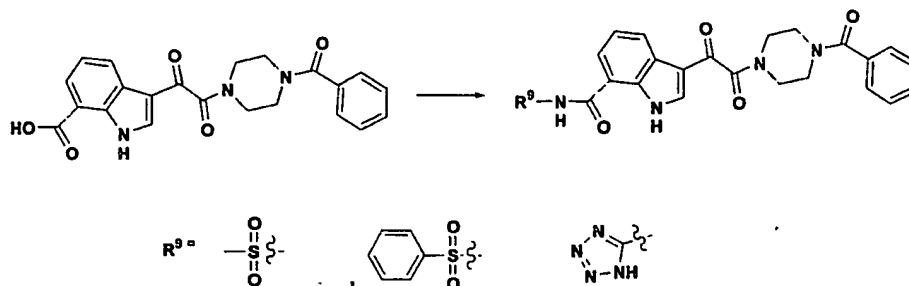
5

Scheme 25A depicts amide formation from either sulfonamide derivatives or amines. The transformation was carried out as follows: To a suspension of the acid shown above (Reference 102, 30 mg, 0.074 mmol)

10   and sulfonamide (such as methylsulfonamide or phenylsulfonamide) or amine (such as 3-aminotetrazole) (0.296 mmol) in CH_2Cl_2 (1 mL), was added DMAP (36 mg, 0.295 mmol) and EDC (56 mg, 0.293 mmol). The resulting mixture was stirred at rt for 16 h, and then evaporated *in vacuo*. The residue was dissolved in MeOH, and subjected to preparative reverse phase HPLC

15   purification.

Scheme 25B
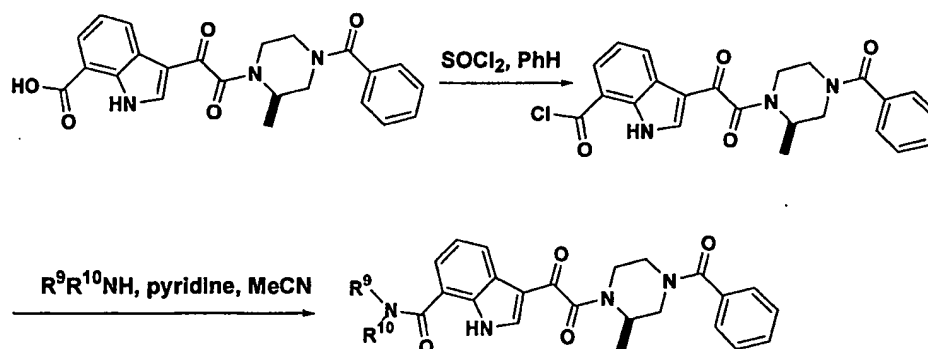
The general procedure for making compounds of Formula I as

20   depicted in Scheme 25B is as follows:

The crude acid chloride was obtained by refluxing a mixture of the acid (Reference 102) shown and excess $SOCl_2$ (1.0 mL per 0.03 mmol of

67

acid) in benzene (15 mL) for 3 h, followed by evaporation of the volatile. A mixture of the acid chloride (30.0 mg, 0.07 mmol) and excess amine (0.14 to 0.22 mmol, 1.0 mL of a 2 *M* solution of methylamine in MeOH for example) in CH$_3$CN (7.0 mL) was stirred at rt for 10 min. After adding excess pyridine
5   (1.0 mL, 12 mmol), the mixture was stirred overnight and then evaporated *in vacuo* to give a residue. The residue was dissolved in MeOH and subjected to purification by preparative reverse phase HPLC.

The above reaction can also be run without solvent. For example, a
10   mixture of the acid chloride (*ca.* 0.03 mmol) in neat ethylamine (0.5 mL, 7.6 mmol) was stirred at rt for 2 h. The excess amine was then removed by evaporation *in vacuo* to give a residue, which was dissolved in MeOH and subjected to purification by preparative reverse phase HPLC.

15   Scheme 25C below provides an example of how a simple methyl amide can be prepared.

68
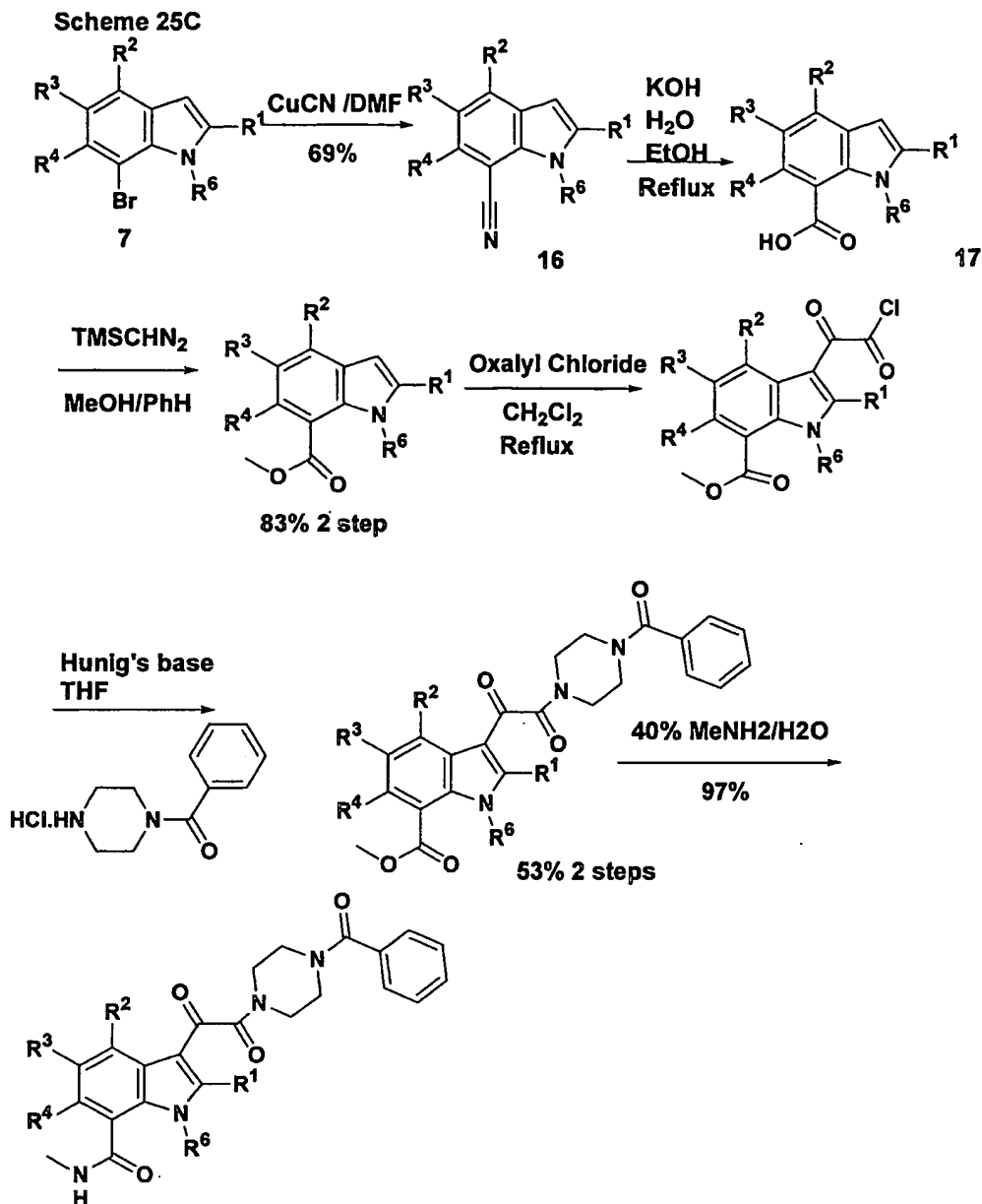
Scheme 25C

Scheme 25D shows a method of using the acid of Formula 39 to
prepare of oxadiazoles of Formula 41 (isomers of Formula 34b). The acid 39
5   is coupled to hydroxyamidine (R represents a suitable heteroaryl substituent)
using EDC as activating agent in an inert solvent (e.g. CH_2Cl_2). The
intermediate amidino ester is then cyclized in the presence of pyridine at
elevated temperature to give oxadiazoles of Formula 41.

Scheme 25D
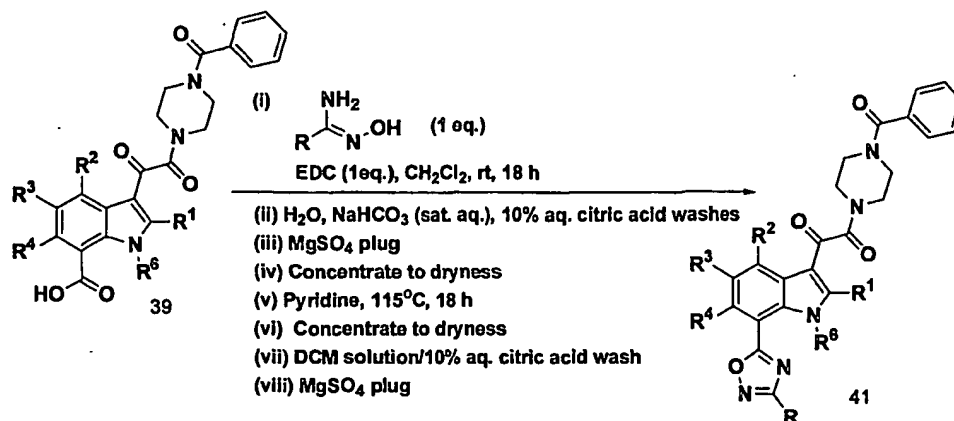
In addition to the use of "Weinreb Amide" of Formula 38 to generate
ketones as described above, aldehydes of Formula 14 could also be used for
5   this purpose. As shown in Scheme 26a, aldehydes of Formula 14 could
react with organometallic reagents (e.g. Grignard reagents such as R^8MgBr,
or organolithium reagents such as R^8Li) in Step a20 to form an alcohol of
Formula 42, which could then be oxidized in Step a21 to give the ketones of
Formula 43. Numerous reaction conditions for organometallic addition to
10 aldehydes and oxidation of secondary alcohols to ketones are well known to
the art and are also provided in reference 91.

Scheme 26a

70
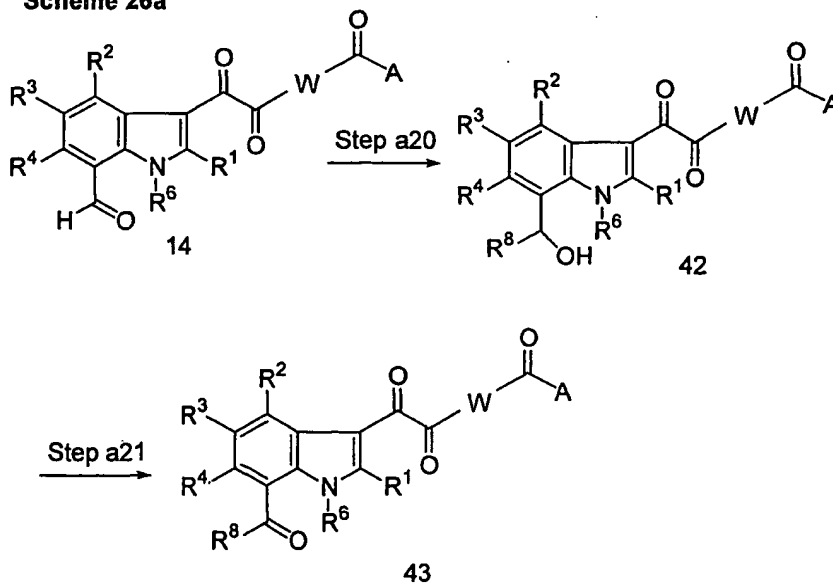
Another method for the preparation of ketones of Formula 43 is shown in Scheme 26b. Nitriles of Formula 22 could react with organometallic reagents (e.g. Grignard reagents, lithium reagents) to give ketones after hydrolytic work up.

5

Scheme 26b
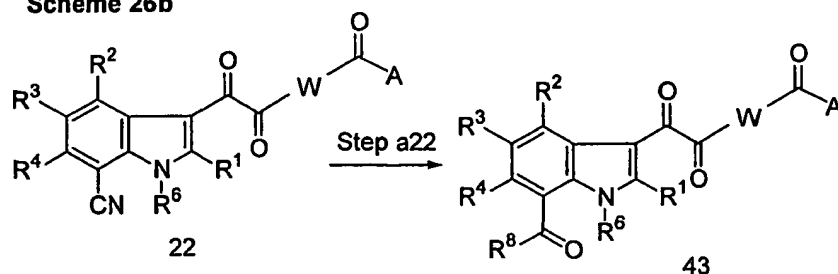
Alternatively, nitriles of Formula 16 can be converted first to ketones by organometallic addition followed by hydrolytic work up. Scheme 26c
10   provides an example of the synthesis of compounds of Formula 46 starting from nitriles of Formula 16.

Scheme 26c
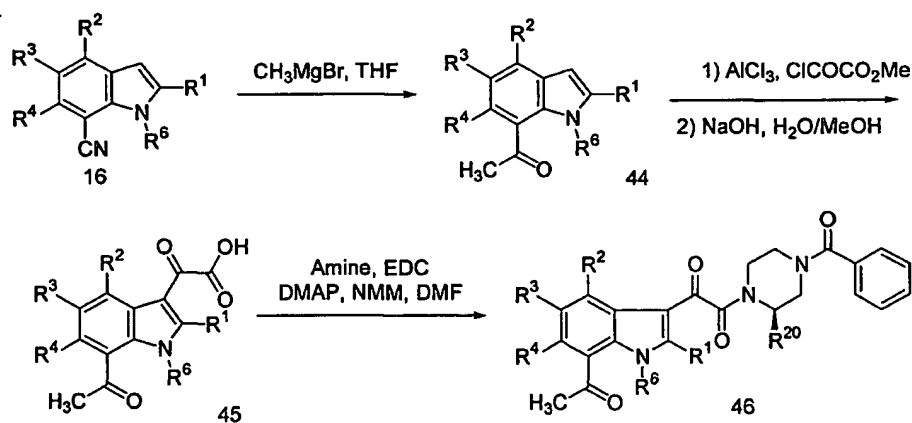
15   Other methods are known in the art and could be employed or modified by one with the skill in the art in the preparation of ketones of Formula 43. These methods include but not limited to (1) Friedel-Crafts type reaction of an indoline or indole with an nitrile, an acid chloride or a N,N-dimethylamide (Reference 105); (2) ortho-metallation of N-Boc protected
20   aniline followed by quenching with a suitable electrophile, e.g. Weinreb amide (Reference 106); (3) reaction of indoyl organometallic reagents with a

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suitable electrophile, e.g. Weinreb amide (Reference 107); (4) the use of a substituted phenone as indole precusor (Reference 108).

Scheme 27
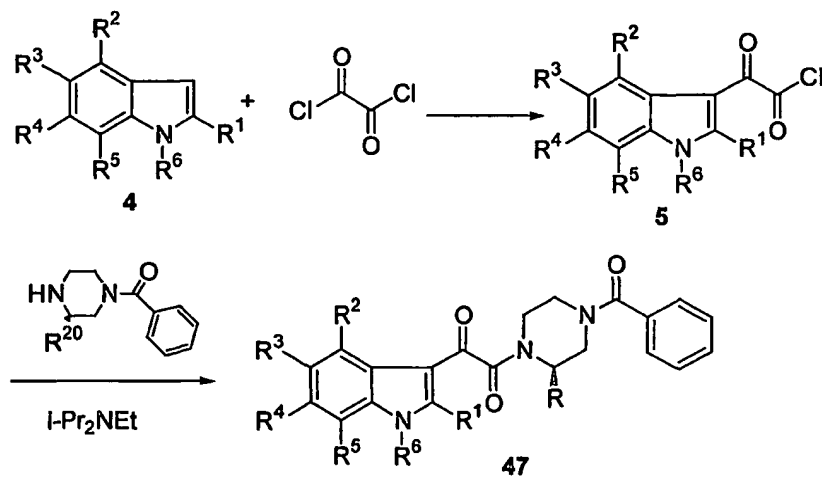
5   The remaining schemes provide additional background, examples, and conditions for carrying out this invention. Specific methods for preparing W and modifying A are presented. As shown in Scheme 27, the indoles 4 are treated with oxalyl chloride in either THF or ether to afford the desired glyoxyl chlorides 5 according to literature procedures (Lingens, F. et al, Ref. 25).

10   The intermediate glyoxyl chlorides 5 are then coupled with benzoyl piperazine (Desai, M. et al, Ref. 26) under basic conditions to afford 47.

Scheme 28
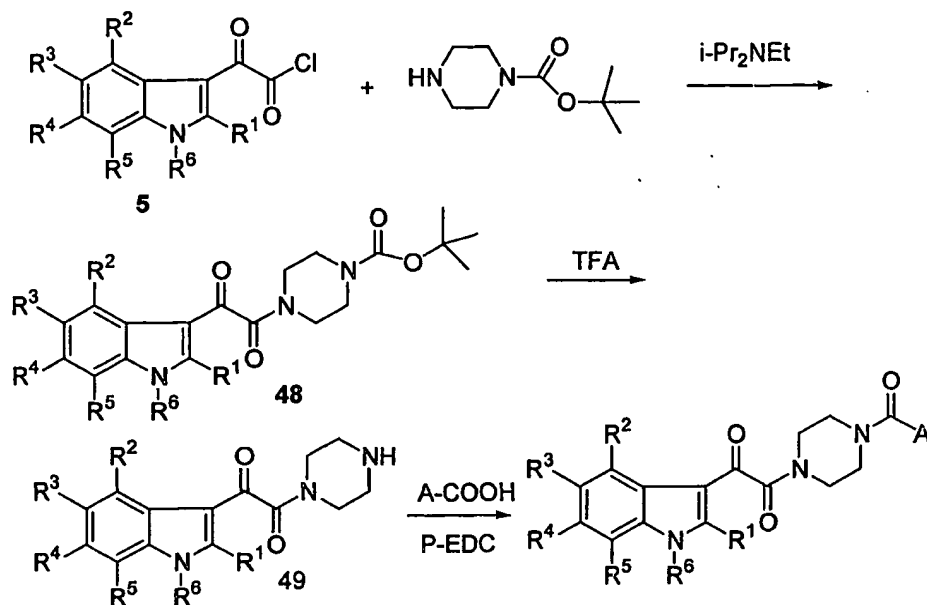
Treatment of indole-3-glyoxyl chloride, 5, (Scheme 28) with *tert*-butyl
1-piperazinecarboxylate affords the piperazine coupled product, 48. It is
5   apparent to one skilled in the art that use of an alternative Boc protected
piperazine which are synthesized as shown below would provide compounds
of formula I with alternative groups of formula W. As discussed earlier, other
amine protecting groups which do not require acidic deprotection conditions
could be utilized if desired. Deprotection of the Boc group of is effected with
10   20% TFA/CH$_2$Cl$_2$ to yield the free piperazine, 49. This product is then
coupled with carboxylic acid in the presence of polymer supported 1-(3-
Dimethylaminopropyl)-3-ethylcarbodiimide (P-EDC) to afford products of
Formula I. This sequence provides a general method for synthesizing
compounds of varied group A in formula I.
15

73
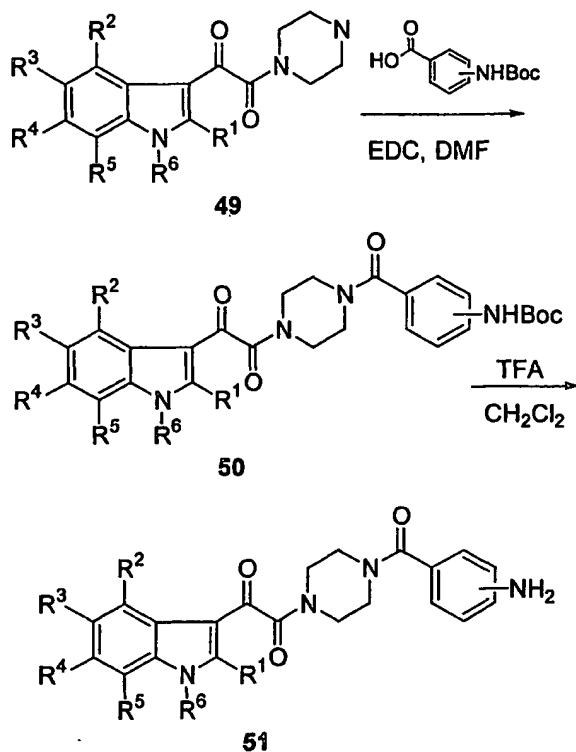
Scheme 29

An example for preparing compounds of Formula I which possess
substituents in A (or other parts of the molecule) which might interfere with
5   the standard reactions is shown in scheme 29. piperazine 49 (Scheme 29)
was treated with Boc-protected aminobenzoic acid in the presence of EDC to
afford 50. A portion of the resulting product was separated and subjected to
TFA in order to remove the Boc group, thus yielding amino derivatives 51.

Scheme 30

10

74
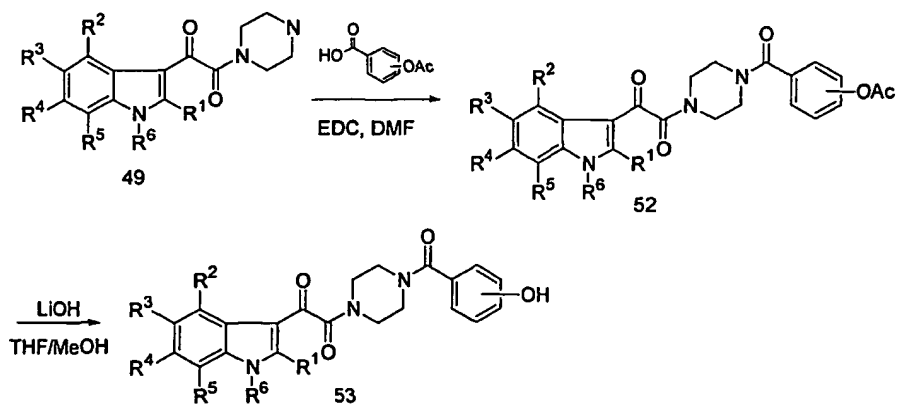
Similarly, substituents which possess a reactive alcohol can be incorporated as below. Piperazine 49 (Scheme 30) was treated with acetoxybenzoic acid in the presence of EDC to afford 52. A portion of the resulting product was separated and subjected to LiOH hydrolysis in order to
5   remove the acetate group, thus yielding hydroxy derivatives 53.

Examples containing substituted piperazines are prepared using the general procedures outlined in Schemes 31-38. Substituted piperazines are either commercially available from Aldrich, Co. or prepared according to
10   literature procedures (Behun et al, Ref. 31(a), Scheme 31, eq. 01). Hydrogenation of alkyl substituted pyrazines under 40 to 50 psi pressure in ethanol afforded substituted piperazines. When the substituent was an ester or amide, the pyrazine systems could be partially reduced to the tetrahydropyrazine (Rossen et al, Ref. 31(b), Scheme 31, eq. 02). The
15   carbonyl substituted piperazines could be obtained under the same conditions described above by using commercially available dibenzyl piperazines (Scheme 31, eq. 03).

Scheme 31

eq. 01

X = OR, NRR

eq. 02

X = OR, NRR

eq. 03
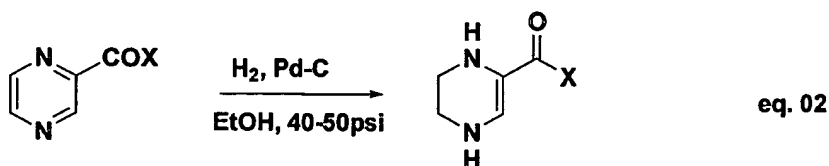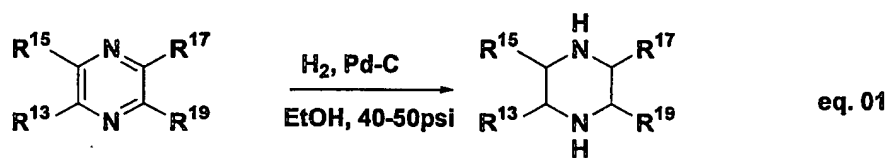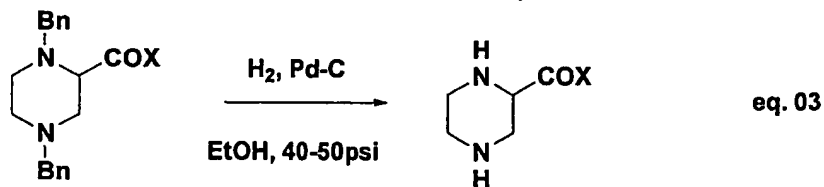
20

2-Trifluoromethylpiperazine (Jenneskens et al., Ref. 31c) was prepared through a four step route (Scheme 32). Using Lewis acid $TiCl_4$,

N,N'-dibenzylethylenediamine 54 reacted with trifluoropyruvates to afford hemiacetal 55, which was reduced at room temperature by Et_3SiH in CF_3COOH to lactam 56. $LiAlH_4$ treatment then reduced lactam 56 to 1,4-dibenzyl-2-trifluoromethylpiperazine 57. Finally, hydrogenation of compound

5   57 in HOAc gave the desired product 2-trifluoromethylpiperazine 58.

Scheme 32
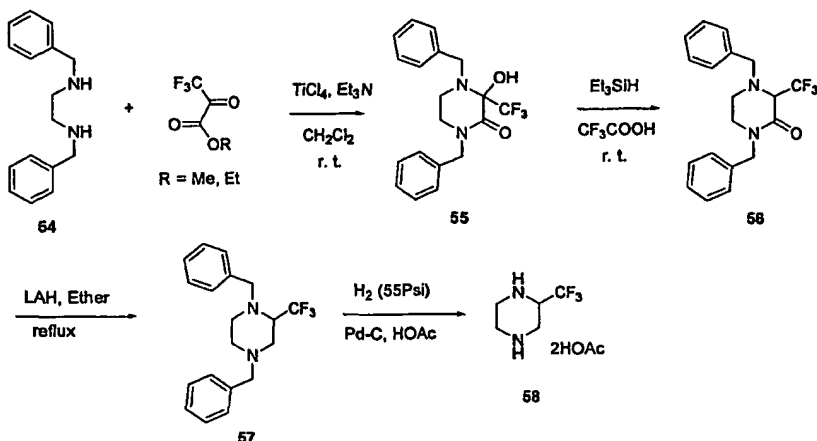
Mono-benzoylation of symmetric substituted piperazines could be achieved by using one of the following procedures (Scheme 33). (a)

10   Treatment of a solution of piperazine in acetic acid with acetyl chloride afforded the desired mon-benzoylated piperazine (Desai et al. Ref. 26, Scheme 33, eq. 04). (b) Symmetric piperazines were treated with 2 equivalents of n-butyllithium, followed by the addition of benzoyl chloride at room temperature (Wang et al, Ref. 32, Scheme 33, eq. 05).

Scheme 33

A , B = alkyl substituents

A , B = hydrogen or alkyl substituents

15
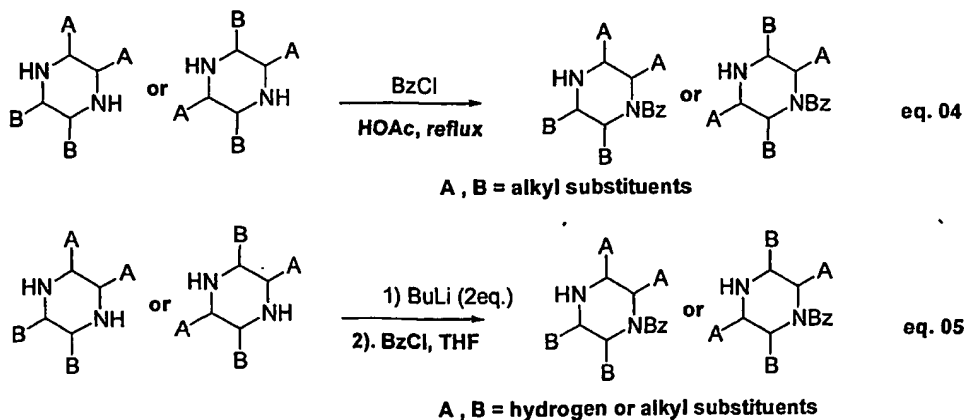
Mono-benzoylation of unsymmetric substituted piperazines (A and B in Scheme 33 represent, for example R^{14}, R^{16}, R^{18} and R^{20} once incorporated into a compound of Formula I) could be achieved by using one of the following procedures (Scheme 33), in which all the methods were exemplified

5 by mono-alkyl substituted piperazines. (a) Unsymmetric piperazines were treated with 2 equivalents of n-butyllithium, followed by the addition of benzoyl chloride at room temperature to afford a mixture of two regioisomers, which could be separated by chromatography (Wang et al, Ref.32 and 33(b), Scheme 34 eq. 06); (b) Benzoic acid was converted to its pentafluorophenyl

10 ester, and then further reaction with 2-alkylpiperazine to provide the mono-benzoylpiperazines with the benzoyl group at the less hindered nitrogen (Adamczyk et al, Ref. 33(a), Scheme 34, eq. 07); (c) A mixture of piperazine and methyl benzoate was treated with dialkylaluminum chloride in methylene chloride for 2-4 days to yield the mono-benzoylpiperazine with the benzoyl

15 group at the less hindered nitrogen (Scheme 34 eq. 08); (d) Unsymmetric piperazines were treated with 2 equivalents of n-butyllithium, followed by subsequent addition of triethylsilyl chloride and benzoyl chloride in THF at room temperature to afford mono-benzoylpiperazines with the benzoyl group at the more hindered nitrogen (Wang et al, Ref. 33(b), Scheme 34, eq. 09).

20 When the substituent at position 2 was a ester or amide, the mono-benzoylation with benzoyl chloride occurred at the less hindered nitrogen of the piperazine with triethylamine as base in THF (Scheme 34, eq. 10).

Scheme 34

eq. 06

eq. 07

eq. 08

eq. 09

eq. 10
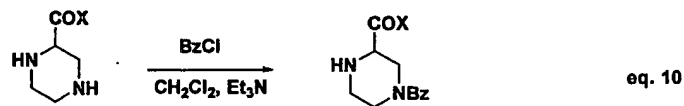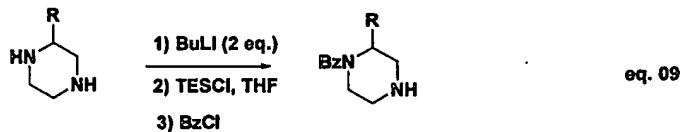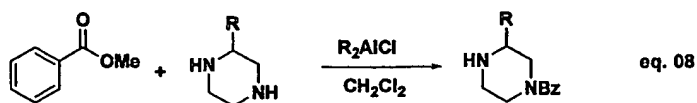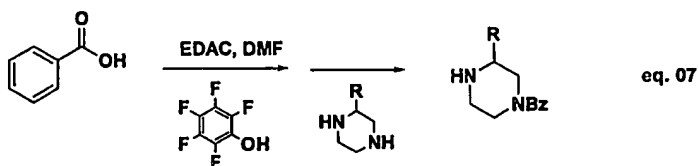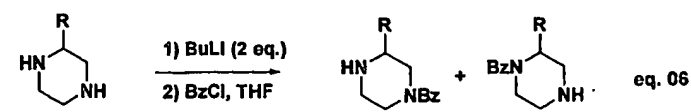
X = OR, NR$_1$R$_2$

In the case of tetrahydropyrazines (Scheme 35, eq. 11), mono-benzoylation occurred at the more hindered nitrogen under the same conditions as those in equation 10 of Scheme 34, in the well precedented manner. (Rossen et al, Ref. 31(b)).

Scheme 35

eq. 11
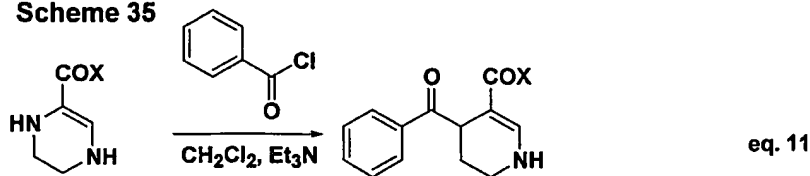
X = alkoxy, amino and substituted amino

Furthermore, the ester group can be selectively reduced by NaBH$_4$ in the presence of the benzamide (Masuzawa et al, Ref. 34), which is shown in Scheme 36.

Scheme 36

R is C$_{1-4}$alkyl

eq. 12
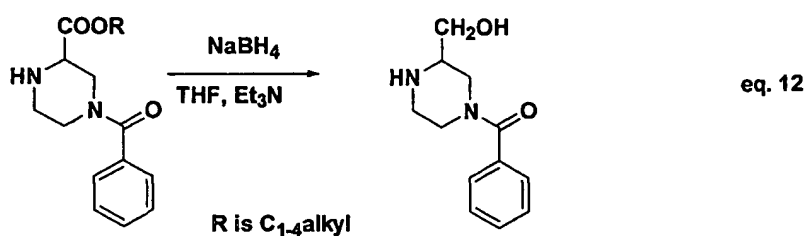
The ester groups on either the piperazine linkers or on the indole
nucleus could be hydrolyzed to the corresponding acid under basic
conditions such as K$_2$CO$_3$ (Scheme 37, eq. 13) or NaOMe (Scheme 37, eq.
14) as bases in MeOH and water.

Scheme 37

eq.13

R' is H or C$_{1-6}$alkyl

eq. 14

Scheme 38

R is C$_{1-6}$alkyl
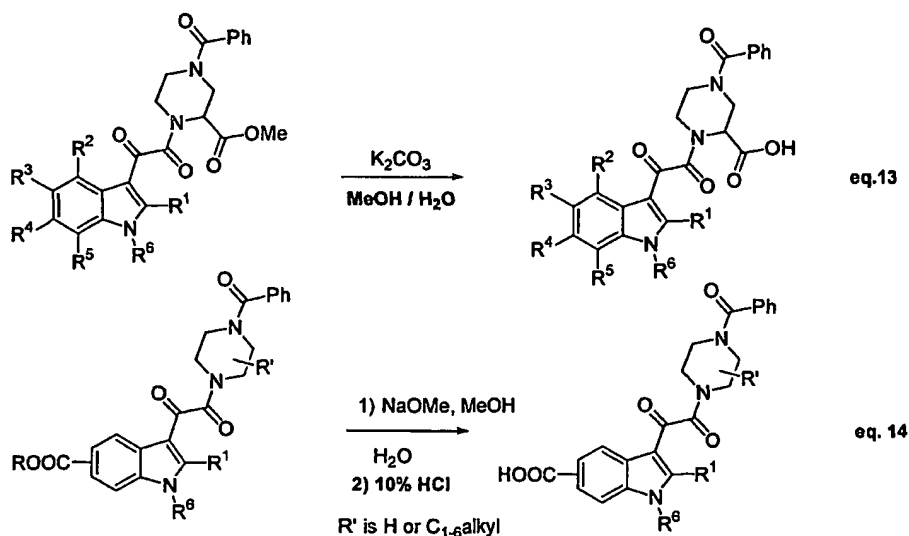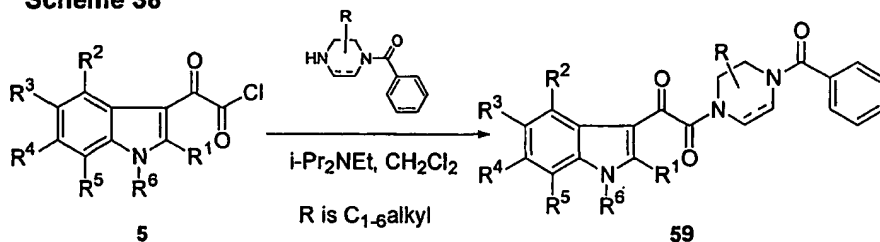
Reaction of glyoxyl chloride 5 with substituted benzoyl piperazines or
tetrahydropyrazines in CH$_2$Cl$_2$ using i-Pr$_2$NEt as base afforded the coupled
products 59.

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In the case of coupling reactions using 3-hydroxylmethyl-benzoylpiperazine, the hydroxyl group was temporarily protected as its TMS ether with BSTFA (N,O-bistrimethylsilyl)fluoroacetamide) (Furber et al, Ref. 35). The unprotected nitrogen atom was then reacted with glyoxyl chlorides
5 5 to form the desired diamides. During workup, the TMS masking group was removed to give free hydroxylmethylpiperazine diamides 60 (Scheme 39).

Scheme 39
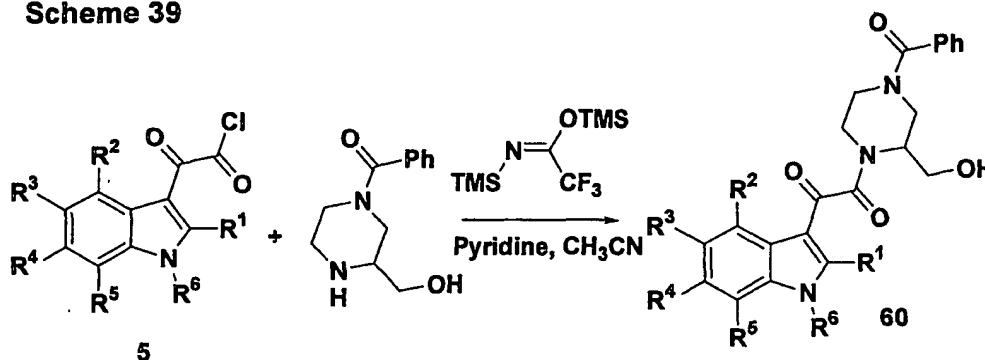
10   Piperazine intermediates were prepared using standard chemistry as shown in Schemes 40 and 41.

Scheme 40

X = CH; intermediate 19
X = N; intermediate 18

Scheme 41

X = CH; intermediate 21
X = N; intermediate 20
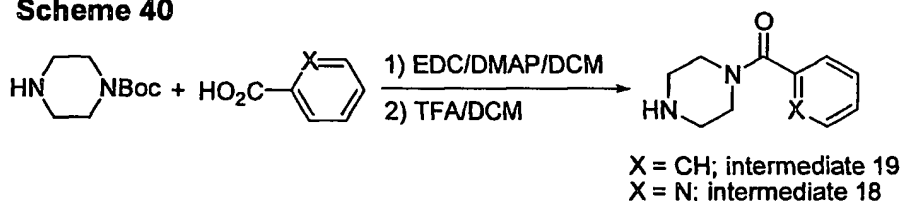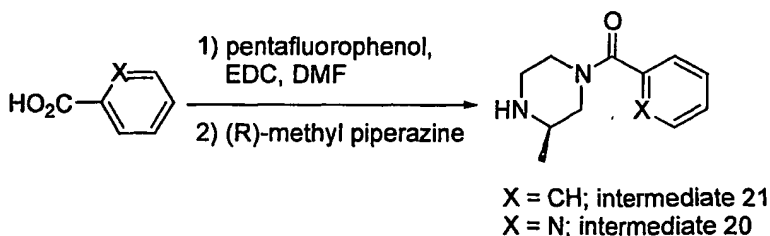
15

Throughout the chemistry discussion, chemical transformations which are well known in the art have been discussed. The average practioner in the art knows these transformations well and a comprehensive list of useful
20 conditions for nearly all the transformations is available to organic chemists and this list is contained in reference 91 authored by Larock and is incorporated in its entirety for the synthesis of compounds of Formula I.

DESCRIPTION OF SPECIFIC EMBODIMENTS

Experimental Section

5   Unless otherwise stated, solvents and reagents were used directly as obtained from commercial sources, and reactions were performed under an nitrogen atmosphere. Flash chromatography was conducted on Silica gel 60 (0.040-0.063 particle size; EM Science supply). ^{1}H NMR spectra were recorded on Buker DRX-500 at 500 MHz (or Buker DPX-300/Varian Gemini

10   300 at 300 MHz as stated). The chemical shifts were reported in ppm on the δ scale relative to δTMS = 0. The following internal references were used for the residual protons in the following solvents: $CDCl_3$ (δ_H 7.26), CD_3OD (δ_H 3.30) and DMSO-d_6 (δ_H 2.50). Standard acronyms were employed to describe the multiplicity patterns: s (singlet), d (doublet), t (triplet), q (quartet),

15   m (multiplet), b (broad), app (apparent). The coupling constant (J) is in hertz. LC/MS was performed on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-VIS detector with Mass Spectrometry data determined using a Micromass LC Platform in positive electrospray mode (ES+). The analytical reverse phase HPLC method is as follow unless otherwise noted:

20   Column YMC ODS-A C18 S7 (3.0 x 50 mm), Start %B = 0, Final %B = 100, Gradient Time = 2 min, Flow rate 5 ml/min. Wavelength = 220 nm, Solvent A = 10% MeOH - 90% H_2O – 0.1% TFA, Solvent B = 90% MeOH - 10% H_2O – 0.1% TFA; and R_t in min. Preparative reverse phase HPLC was performed on a Shimadzu LC-8A automated preparative HPLC system with detector

25   (SPD-10AV UV-VIS) wavelength and solvent systems (A and B) the same as above.

For examples 195 through 214, the following methodology was used to obtain the LC retention times and mass spectral data. The methods were

30   run on a MUX HPLC-MS instrument (MS8) comprising:
Waters 600E HPLC pump and controller, Gilson Multiprobe liquid handler, Gilso889 injector module, Waters 2487 UV detectors (x8) fitted with micro-flow cells, and a Micromass LCT mass spectrometer with MUX 8 way interface. The HPLC pump delivers rhe mobile phase at 8 ml/min to an 8

35   way splitter where the flow is distributed to eight flow lines. The flow down each line is proportional to the back pressure of that line and is nominally 1mL/min. Post splitter, the flow runs to eight Rheodyne injectors mounted in

one unit and then into eight identical HPLC columns and eight UV detectors. The HPLC eleunt from each detector is split and approximately 30-80uL/min per line enters the MUX interface housing attached to the LCT mass spectromphotometer. The HPLC pump, liquid handler, injector module, and

5   mass spectrometer are controlled using the MicroMass Mass Lynx software under Windows NT. The eight UV detectors are operated manually from their fronmt panels but do receive auto zero signals from the injector module. Analogue signals from the UV detectors are fed both into the Mass Lynx software, via connectors on the mass spectrometer, and also into the

10 Millenium Chromatography Data System via standard SAT/IN and LACE interfaces. Samples are prepared at concentrations of 0.5 mg /mL in acetonitrile water. The following HPLC conditions are used: Mobile Phase: Aqueous, Water +0.1+ TFA; Organic, Acetonitrile + 0.1% TFA. Column : Hypersil BDS C18, 50mmx2.1mmid.,5μ packing.

15 Gradient:

Time (min)	% Organic	Curve
0.00	12	1
0.80	60	6
1.80	95	6
2.10	12	6
2.40	12	6

Run time: 2.4 min. Flow rate: 8.0 mL/min, split eight ways to each column. Injection volume: 30μL into a 5μL loop, filled loop method.

I. Preparation of Intermediates

INTERMEDIATE 1 (example of Scheme 3)
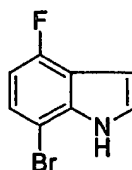
5

A solution of 2-bromo-5-fluoronitrobenzene (4.4 g, 20 mmol) in dry
THF (200 mL) under N_2 was cooled to -65 °C (acetone/CO_2). A solution of
vinylmagnesium bromide (60 mL, 1 M, 60 mmol) in THF was added to the
10   nitrobenzene solution as rapidly as possible maintaining the reaction
temperature below -40 °C. After addition of the Grignard reagent, the cooling
bath was switched to a -40 °C bath (CH_3CN/CO_2), and the mixture was
stirred at -40 °C for 30 min. The reaction mixture was quenched with sat.
NH_4Cl solution (500 mL) and extracted with ether (2 x 200 mL), then dried
15   (brine, Na_2SO_4) and concentrated in vacuo. The resulting material was
purified by SiO_2 flash column chromatography (5:95) EtOAc / Hexanes to give
4-fluoro-7-bromoindole, as a light brown oil (2.03 g, 9.5 mmol, 54%). [1]H
NMR ($CDCl_3$) δ 6.72 (m, 2 H), 7.24 (m, 2 H), 8.4 (br s, 1 H). MS m/e 215
(MH^+).

INTERMEDIATE 2
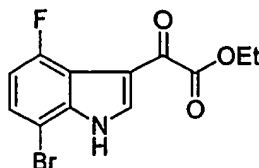
5   To a solution of ethyl chlorooxoacetate (1.397 g, 10.25 mmol) and 4-Fluoro-7-bromoindole (1.1 g, 5.14 mmol) in CH_2Cl_2 (10mL) at 0°C was added aluminum chloride (1.367 g, 10.25 mmol). The mixture was stirred for 1h at 0°C then quenched with 1 N HCl. The mixture was extracted with CH_2Cl_2 and the organic layers concentrated in vacuo. The crude material was

10   purified by SiO_2 flash column chromatography (gradient 10-30%) EtOAc / Hexanes to give the ester, intermediate 2, as a yellow solid (846 mg, 2.69 mmol, 52%). ^1H NMR ($CDCl_3$) δ 1.43 (t, J = 6.9 Hz, 3 H), 4.42 (q, J = 6.9 Hz, 1 H), 6.92 (m, 1 H), 7.40 (m, 1 H), 8.42 (d, J = 3 Hz, 1 H), 9.04 (br s, 1 H).

15   **INTERMEDIATE 3**
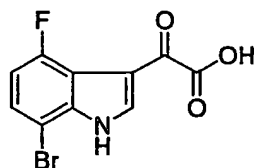
      The ester, intermediate 2, was directly hydrolyzed in MeOH (10 mL) with 1 N NaOH (5.4 mL, 5.4 mmol) at reflux temperature for 15 min. The

20   sodium salt was treated with 1 N HCl (5.4 mL, 5.4 mmol) and the solvents were removed in vacuo to give the free acid, intermediate 3, as a white solid.

INTERMEDIATE 4
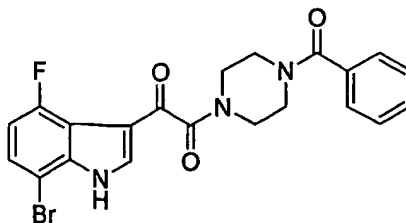
A mixture of the acid, intermediate 3; (2.69 mmol)], N-benzoyl piperazine (563 mg, 2.96 mmol), EDC·HCl (622 mg, 3.24 mmol), N-methylmorpholine (330 mg, 3.24 mmol), and hydroxybenzotriazole (405 mg, 2.96 mmol) in DMF (5 mL) was stirred at ambient temperature for 2 h then

5 warmed to 90 °C for 30 min. The mixture was poured into water and extracted into EtOAc. The EtOAc layers were dried (brine, MgSO₄) and concentrated in vacuo. The resulting material was purified by SiO₂ flash column chromatography (gradient 40-100%) EtOAc / Hexanes to give intermediate 4 as a white solid (250 mg, 0.55 mmol, 20%). ^{1}H NMR (CDCl₃)

10 δ 3.5 (m, 4 H), 3.75 (m, 4 H), 6.85 (m, 1 H), 7.35 (m, 1 H), 7.39 (m, 5 H), 8.06 (d, J = 3.3 Hz, 1 H). MS m/e 458, 460 (MH⁺).

INTERMEDIATE 5
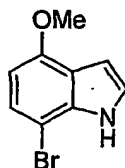
15

4-Methoxy-7-bromoindole, was prepared in the same manner as 4-fluoro-7-bromoindole, (intermediate 1) in 38% yield. ^{1}H NMR (CDCl₃) δ 3.95 (s, 3 H), 6.44 (d, J = 4.8 Hz, 1 H), 6.73 (s, 1 H), 7.17 (s, 1 H), 6.24 (d, J = 4.8

20 Hz, 1 H), 8.4 (br s, 1 H). MS m/e 223.9, 225.9 (M-H⁻). Anal. Calcd for C₉H₈BrNO: C, 47.82; H, 3.57; N, 6.20; Found: C, 47.91; H, 3.56; N, 6.11.

INTERMEDIATE 6
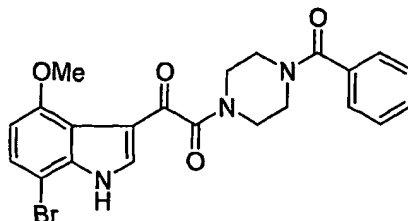
25

4-methoxy-7-bromoindole, intermediate 5, (1.06 g, 4.71 mmol) was dissolved in THF (10 mL) and oxalyl chloride (3 g, 23.6 mmol) was added.

85

The mixture was stirred at ambient temperature for 5 h then at 50 °C for 30 min. The volatile solvents were removed in vacuo leaving a green solid, which was used directly in the next step. The acid chloride was dissolved in THF (20 mL) and N-benzoyl piperazine (1070 mg, 5.65 mmol) was added

5 followed by diisopropylethylamine (1220 mg, 9.42 mmol). The mixture was stirred at ambient temperature for 18 h then heated to reflux temperature for 30 min. The mixture was poured into water and extracted into EtOAc. The EtOAc layers were dried (brine, MgSO$_4$) and concentrated in vacuo. The resulting material was purified by SiO$_2$ flash column chromatography

10 (gradient 50-80%) EtOAc / Hexanes to give intermediate 6 as a slightly yellow solid (520 mg, 1.1 mmol, 23%). ^{1}H NMR (CDCl$_3$) δ 3.5 (m, 4 H), 3.75 (m, 4 H), 3.92 (s, 1H), 6.60 (d, J = 5 Hz, 1 H), 7.33 (d, J = 5 Hz, 1 H), 7.43 (m, 5 H), 8.03 (s, 1 H), 9.07 (br s, 1 H). MS m/e 470, 472 (MH$^+$). HPLC R$_t$ = 1.347.

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INTERMEDIATE 7
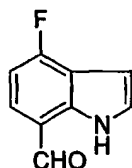
20 To a THF solution (15 mL) of 4-fluoro-7-bromoindole, intermediate 1 (1 g, 4.67 mmol) at - 78 °C was added n-butyllithium (5.6 mL, 2.5 M, 14 mmol) dropwise over 15 min. The mixture was warmed to 5 °C and stirred for 30 min before cooling back down to -78 °C. DMF (1.8 mL, 23.2 mmol) was added and the mixture was warmed to ambient temperature for 15 min. The

25 solution was poured into water and extracted into EtOAc. The EtOAc layers were dried (brine, MgSO$_4$) and concentrated in vacuo. The resulting material was purified by SiO$_2$ flash column chromatography (1:4) EtOAc / Hexanes to give intermediate 7 as a slightly yellow solid (403 mg, 2.48 mmol, 53%). ^{1}H NMR (CDCl$_3$) δ 6.71 (d, J = 2 Hz, 1 H), 6.92 (t, J = 4.9 Hz, 1 H), 7.33 (t, J =

30 1.7 Hz, 1 H), 7.63 (dd, J = 2.9, 4.9 Hz, 1 H), 10.05 (s, 1 H), 10.25 (br s, 1 H).

INTERMEDIATE 8
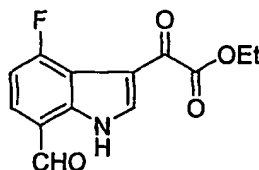
5   Intermediate 7 (2.27 g, 13.92 mmol) and ethyl chlorooxoacetate (3.2 mL, 27.85 mmol) were dissolved in CH_2Cl_2 (25mL). The solution was cooled to 0 °C and aluminum chloride was added portionwise (3.71 g, 27.85 mmol) followed by an additional 15 mL of CH_2Cl_2. The mixture was stirred at 0 °C for 30 min then warmed to ambient temperature for 1 h, and recooled to 0 °C

10   before quenching with 1 N HCl. The solution was poured into water and extracted into EtOAc. The EtOAc layers were dried (brine, $MgSO_4$) and concentrated in vacuo. The resulting material was crystallized from EtOAc / Hexanes to give intermediate 8 as a slightly yellow solid (2.72 g, 10.34 mmol, 74%).

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INTERMEDIATE 9
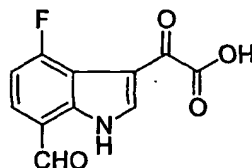
20   Aqueous NaOH (2.07 mL, 10 N, 20.7 mmol) was added to an EtOH solution (10 mL) of the ester, intermediate 8, (2.72 g, 10.34 mmol) and the mixture was stirred at ambient temperature for 2 h. Aqueous 6 N HCl was added until the pH was approximately 2. The EtOH was removed in vacuo and the solid remaining was filtered and washed with cold water followed by

25   dry ether to give the acid, intermediate 9 (2.27 g, 9.66 mmol, 93%).

INTERMEDIATE 10
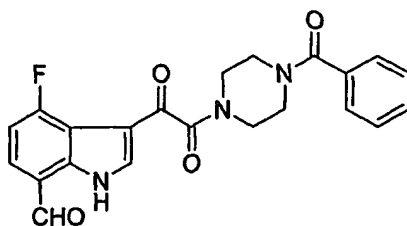
5   Prepared from intermediate 9 as described in Reference 102.

INTERMEDIATE 11

10
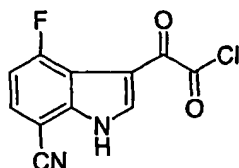
To a solution of 4-fluoro-7-cyanoindole (Reference 102, 350 mg, 2.18 mmol) in CH_2Cl_2 (14 ml) was added oxalyl chloride (7.0 ml, 80.2 mmol). The mixture was heated to reflux for 3 days, and then concentrated in vacuo to afford intermediate 11 as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD) δ 8.51
15   (s, 1H), 7.74 (app dd, J = 8.5, 4.2, 1H), 7.12 (app dd, J = 10.1, 8.5, 1H).

INTERMEDIATE 12
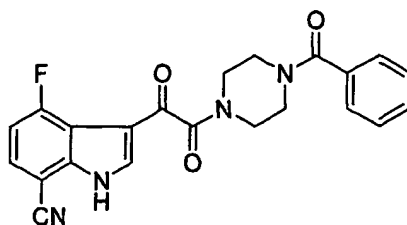
20

To a solution of indole, intermediate 11, in THF (15 mL), was added intermediate 19 (596 mg, 2.63 mmol) and N, N-diisopropylethylamine (3.8 mL, 21.8 mmol). The resulting mixture was stirred at rt for 16 h. After quenching with MeOH (15 mL), the reaction mixture was concentrated in
25   vacuo to give a brownish oil, which was subjected to flash chromatography

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using a gradient elution (50% to 90% EtOAc/Hexane) to give intermediate 12 as a white solid (550 mg, 62% two steps). ^{1}H NMR (CDCl$_3$) δ 10.39 (s, 1H), 8.18 (d, J = 3.3, 1H), 7.64 (app dd, J = 8.2, 4.4, 1H), 7.45 (b s, 5H), 7.08 (app t, J = 9.3, 1H), 4.00 – 3.45 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 405, HPLC
5   R$_t$ = 1.243.

INTERMEDIATE 13

10
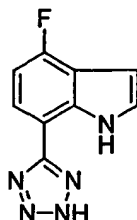
      To a solution of 4-fluoro7-cyanoindole (300 mg, 1.87 mmol) in DMF (6 ml) were added ammonium chloride (386 mg, 6.18 mmol) and sodium azide (365 mg, 5.62 mmol). After stirring at 100 °C for 17 h, the reaction mixture was cooled to rt and quenched carefully with excess hydrochloric acid (10
15   mL, 1N aq.). The mixture was then diluted with water (~50 mL) to induce precipitation. The light brown precipitates were filtered, washed with 3 times of excess water and dried under high vacuum to provide the tetrazole, intermediate 13 (338.5 mg, 89%). ^{1}H NMR (CD$_3$OD) δ 7.73 (dd, J = 8.2, 4.6, 1H), 7.45 (d, J = 3.3, 1H), 6.92 (dd, J = 10.0, 8.2, 1H), 6.66 (d, J = 3.3, 1H).
20   LC/MS (ES+) m/z (M+H)$^+$ = 204, HPLC R$_t$ = 1.223.
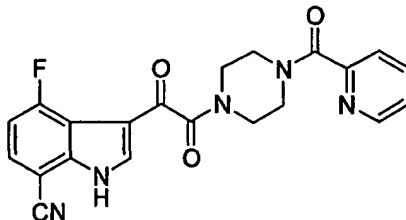
INTERMEDIATE 14

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Prepared in the same manner as intermediate 12.

^{1}H NMR (mixture of conformers, CD$_3$OD) δ 8.64 and 8.55 (app d, J = 4.4, 1H), 8.28 (app d, J = 4.4, 1H), 7.96 (m, 1H), 7.74 (m, 1H), 7.65 (m1H), 7.48 (m, 1H), 7.11 (m, 1H) 3.94 – 3.55 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 406, HPLC R$_t$ = 1.047.

5

INTERMEDIATE 15
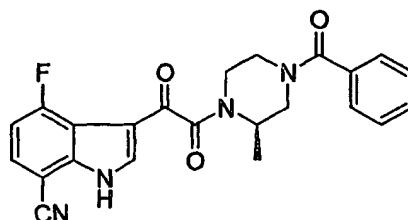
10　　　Prepared in the same manner as intermediate 12.

^{1}H NMR (mixture of conformers, CD$_3$OD) δ 8.29 and 8.23 (app s, 1H), 7.72 (app b s, 1H), 7.46 (app b s, 5H), 7.11 (app b s, 1H), 5.00 – 3.00 (b m, 7H), 1.40 – 1.22 (b m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 419, HPLC R$_t$ = 1.263.

15　　　　　　　　　　## INTERMEDIATE 16
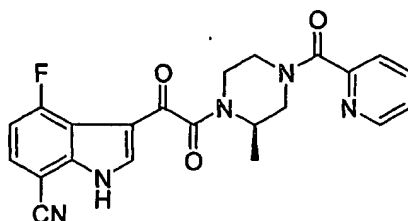
Prepared in the same manner as intermediate 12.

20　^{1}H NMR (CD$_3$OD) δ 8.64 – 8.52 (m, 1H), 8.31 – 8.24 (m, 1H), 8.00 – 7.91 (m, 1H), 7.74 (m, 1H), 7.66 (m,1H), 7.55 – 7.45 (m, 1H), 7.12 (m, 1H), 4.95 – 3.10 (b m, 7H), 1.42 – 1.23 (m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 420, HPLC R$_t$ = 1.127.

90

INTERMEDIATE 17
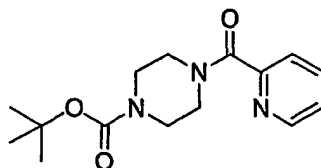
5   To a solution of tert-butyl 1-piperazinecarboxylate (10.0 g. 53.7 mmol) and picolinic acid (6.01 g, 48.8 mmol) in CH_2Cl_2 (300 mL), was added DMAP (6.564 g, 53.7 mmol) and EDC (10.261 g, 53.7 mmol). The reaction mixture was stirred at rt for 16 h, and then washed with hydrochloric acid (5 x 250 mL, 1 *N* aq.) and water (350 mL). The organic layer was dried ($MgSO_4$) and 10   evaporated *in vacuo* to give the N-Boc piperazine, intermediate 17, as white solid (9.9 g, 70%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.56 (app d, *J* = 5.5, 1H), 7.91 (app t, *J* = 6.8, 1H), 7.57 (d, *J* = 6.8, 1H), 7.45 (m, 1H), 3.70 (m, 2H), 3.50 (m, 2H), 3.43 (m, 4H), 1.41 (b s, 9H); LC/MS (ES+) m/z $(M+H)^+$ = 291, $(2M+H)^+$ = 581, HPLC R_t = 1.173.

15

INTERMEDIATE 18
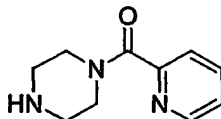
20   To the N-Boc piperazine derivative, intermediate 17, (9.9 g, 34 mmol) was charged a solution of HCl in Dioxane (40 mL, 4 *M*), and the mixture was stirred at rt for 5 h. Removal of the excess reagent *in vacuo* afforded the hydrochloride salt, intermediate 18, as a white solid (100% conversion). ^{1}H NMR (300 MHz, CD_3OD) δ 8.94 (m, 1H), 8.63 (m, 1H), 8.22 (app d, *J* = 7.9, 25   1H), 8.11 (m, 1H); LC/MS (ES+) m/z $(M+H)^+$ = 192, $(2M+H)^+$ = 383, HPLC R_t = 0.113.

91
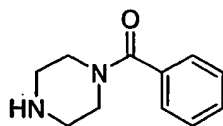
INTERMEDIATE 19

5   Prepared in the same manner as intermediate 18. To a solution of *tert*-butyl 1-piperazinecarboxylate (15.0 g. 80.5 mmol) and benzoic acid (8.94 g, 73.2 mmol) in CH_2Cl_2 (500 mL), was added DMAP (9.84 g, 80.5 mmol) and EDC (15.39 g, 80.5 mmol). The reaction mixture was stirred at rt for 17 h, and then washed with excess hydrochloric acid (5 x 250 mL, 1 *N* aq.) and
10   water (350 mL). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give N-Benzoyl-N'-Boc piperazine as an off white solid (21 g, 99%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.46 (m, 5H), 3.80 – 3.30 (b m, 8H), 1.47 (s, 9H); LC/MS (ES+) m/z $(M+H)^+$ = 291, $(2M+H)^+$ = 581, HPLC R_t = 1.430.

15   To the N-Benzoyl-N'-Boc piperazine was charged a solution of HCl in Dioxane (80 mL, 4 *M*), and the mixture stirred at room temperature for 5 h. The reaction mixture was then concentrated *in vacuo* to afford the hydrochloride salt, intermediate 19, as a white solid (100% conversion). ^{1}H NMR (300 MHz, CD_3OD) δ 7.5 (m, 5H), 4.0 – 3.7 (b, 4H), 3.7 – 3.6 (b m, 4H);
20   LC/MS (ES+) m/z $(M+H)^+$ = 191, $(2M+H)^+$ = 381, HPLC R_t = 0.210.

INTERMEDIATE 20
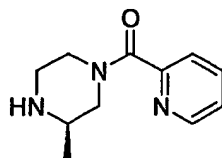
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        To a solution of picolinic acid (4.06 g, 32.9 mmol) and pentafluorophenol (6.06 g, 32.9 mmol) in DMF (50 mL) was added EDC (6.30 g, 32.9 mmol). The reaction mixture was stirred for 4 h at rt until LC/MS analysis showed the complete formation of the intermediate ester. (*R*)-
30   methyl piperazine (3.0 g, 30 mmol) was then added and the resulting mixture stirred at rt for 16 h. Removal of the solvent *in vacuo* afforded a yellow oil, which was subjected to flash chromatography using a gradient elution (50%

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EtOAc/Hexane, to 5% to 15% MeOH/EtOAc, to 1/3/17 NH₃(sat. aq.)/MeOH/EtOAc) to give intermediate 20 as a yellow oil (1.67 g, 27%). ^{1}H NMR (300 MHz, CD₃OD) δ 8.60 (app d, J = 4.7, 1H), 7.98 (m, 1H), 7.60 (m, 1H), 7.5(m, 1H), 4.53 (app d, J = 12.6, 1H), 3.62 (m, 1H), 3.10 – 2.59 (b m, 5H), 1.19 and 1.00 (app d, J = 6.4, 5.4, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 206, (2M+H)$^+$ = 411, HPLC R$_t$ = 0.153.

INTERMEDIATE 21
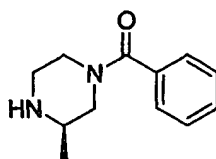
Prepared in the same manner as intermediate 20. ^{1}H NMR (300 MHz, CD₃OD) δ 7.47 (m, 5H), 4.50 (app d, J = 10.6, 1H), 3.59 (b s, 1H), 3.14 – 2.57(b m, 5H), 1.15 – 0.97 (b m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 205, (2M+H)$^+$ = 409, HPLC R$_t$ = 0.310.

INTERMEDIATE 22
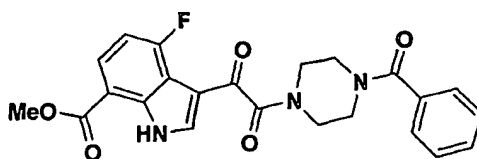
To a solution of methyl (4-fluoro)indole-7-carboxylate (1 eq) in dry THF was added dropwise oxalyl chloride (1.2 eq) at 0 °C. After 5 min., the reaction was warmed to rt and was stirred at rt until completion. The mixture was then concentrated under reduced pressure to provide crude glyoxyl chloride. To a solution of crude 3-glyoxyl chloride of methyl (4-fluoro)indole-7-carboxylate (5.39 mmol) in THF (50 mL) was added intermediate 19 (1.23 g, 5.42 mmol) and diisopropylethylamine (5.6 ml, 32.2 mmol). The reaction mixture was stirred at rt for 14 h, then MeOH (5 mL) was added and the mixture was concentrated in vacuo. The yellow residue was purified by flash chromatography (50% to 100% EtOAc/Hexane) to afford intermediate 22, as a pale yellow solid (1.25 g, 53% based on methyl (4-fluoro)indole-7-

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carboxylate). ^{1}H NMR (CD$_3$OD) δ 8.17 (s,1H), 8.00 (dd, J = 8.0, 4.5, 1H), 7.44 (b, s, 5H), 7.05 (app t, J = 9.0, 1H), 3.99 (s, 3H), 3.84 – 3.51 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 438, HPLC R$_t$ = 1.283.

5   **INTERMEDIATE 23**
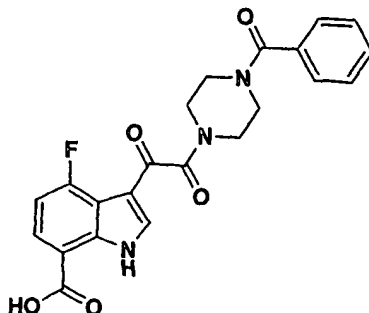
To a solution of intermediate 22, (1.0 g, 2.3 mmol) in MeOH (5 mL)
10   was added NaOH (1N, 5 mL, 1 N, aq.). The reaction mixture was stirred at rt
for 6 h. After which time, 10 pipet drops of NaOH (10 N, aq.) was added, and
the mixture was stirred for an additional 4 h until HPLC analysis showed the
completion of the reaction. The reaction mixture was then acidified to pH 1
using HCl (~5.5 N aq.). The precipitates were collected by filtration, washed
15   with water and dried under high vacuum to give intermediate 23 as a white
solid (837 mg, 86%). ^{1}H NMR (DMSO-d_6) δ 13.45 (b, 1H), 12.34 (s, 1H), 8.08
(app d, J = 3.0, 1H), 7.93 (dd, J = 8.0, 4.0, 1H) 7.44 (b, s, 5H), 7.14 (app t, J
= 9.2, 1H), 3.79 – 3.34 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 424, HPLC R$_t$
= 1.297.

20

Alternatively, the acid, intermediate 23 can be prepared by oxidation
of the carboxaldehyde, intermediate 10, as follows.

AgNO$_3$ (166 mg, 0.98 mmol) was dissolved in water (1 mL). NaOH (79
25   mg, 1.96 mmol) in MeOH/H$_2$O (1:1) was added to this solution, and a brown
precipitate was formed. The aldehyde, intermediate 10, (200 mg, 0.49mmol)]
was added to the above reaction mixture in one portion, and the reaction was
heated at 90~100°C for about 2-3 h. The reaction mixture was then cooled to
rt and filtered through celite. The filter cake was washed with hot water (3x)
30   and the cooled filtrate was extracted with EtOAc. The aqueous extract was

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acidified with 2N HCl to about pH 2. The resulting light grey solid was collected by filtration to yield the acid, intermediate 23, (109 mg).

Intermediate 24

5
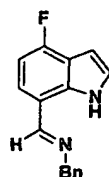
A mixture of 4-fluoro-7-formylindole, **intermediate 7** (100 mg, 0.613 mmol) and benzylamine (0.1 ml, 0.915 mmol) in EtOH (1.5 ml) was stirred at room
10   temperature for 20 hours. After which time, the volatile was evaporated *in vacuo* to give the imine product as a light brown oil. ^{1}H NMR: (CDCl$_3$) δ 10.87 (b s, 1H), 8.58 (s, 1H), 7.39-7.35 (overlapping m, 4H), 7.31-7.25 (overlapping m, 3H), 6.83 (dd, J = 8.0, 10.0, 1H), 6.65 (t, J = 2.7, 1H), 4.88 (2, 2H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 253, HPLC R$_t$ = 1.330.

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Intermediate 25
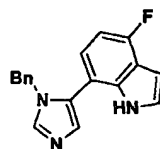
A mixture of the imine, **intermediate 24** (48.3 mg, 0.191 mmol) in DMF (1.0
20   ml) was added TOSMIC (47.3 mg, 0.297 mmol) and powdered K$_2$CO$_3$ (54.7 mg, 0.396 mmol), and the reaction mixture was stirred at room temperature for 72 hours. The mixture was diluted with brine (50 ml) and the resulting white suspension extracted with EtOAc (50 ml). The organic extract was washed with sodium bicarbonate (25 ml, *sat. aq.*), followed by brine (50 ml),
25   dried (MgSO$_4$) and evaporated *in vacuo*. The crude material was purified by preparative TLC (10% MeOH/CH$_2$Cl$_2$, 2 x 500 μm x 20 cm x 20 cm plates) to give the imidazole product as a light yellow oil (26.7 mg, 48% 2 steps). ^{1}H NMR: (CD$_3$OD) δ 7.90 (s, 1H), 7.19 (d, J = 3.2, 1H), 7.15-7.13 (overlapping m, 3H), 7.10 (s, 1H), 6.87 (dd, J = 8.0, 10.2, 1H), 6.82-6.80 (overlapping m,
30   2H), 6.71 (dd, J = 4.9, 8.0, 1H), 6.54 (d, J = 3.2, 1H), 5.08 (s, 2H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 292, HPLC R$_t$ = 1.413.
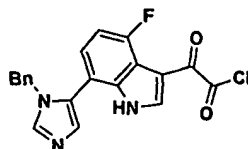
Intermediate 26

5   To the imidazole **intermediate 25** (26.7 mg, 0.092 mmol) was added a
     solution of oxalyl chloride in dichloromethane (1.0 ml, 2.90 mmol, 2 *M*). The
     mixture was stirred at room temperature for 5 hours and the volatile
     evaporated under a stream of nitrogen to give a yellow solid product, which
     was further dried under high vacuum.

10

Intermediate 27

Intermediate 27
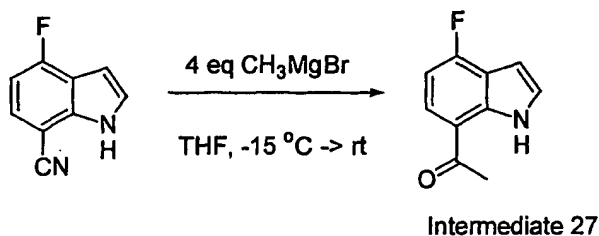
15   To an oven dried 250 ml flask was charged with CH_3MgBr (16.7 ml, 50 mmol,
      3 *M* in Et_2O) at r.t. under N_2. It was then cooled down to −18°C in a NaCl/ice
      bath, and 7-cyano-4-fluoroindole (2.0 g, 12.5 mmol) in dry THF (100 ml) was
      added dropwise using an addition funnel over 45 min. After 10 min, the
      reaction mixture was allowed to warm to r.t., and stirred for 2 hr. The
20   reaction was slowly quenched with 5% sulfuric acid and the mixture stirred
      for 10 min. The reaction mixture was concentrated *in vacuo* and the residue
      poured into $CHCl_3$ (150 ml). After neutralization with aqueous NH_3 (50 ml),
      water (100 ml) was added, and the two layers were separated using a
      separation funnel. The aqueous layer was back extracted with $CHCl_3$ (2 x
25   100 ml), and the combined organic extracts washed with H_2O (100 ml), brine
      (100 ml), and dried ($MgSO_4$). After evaporation *in vacuo*, the resulted crude
      compound was purified by flash chromatography (20% EtOAc/Hexane) to
      give 7-acetyl-4-fluoroindole (1.3 g, 59%) as a light gray solid. ^1H **NMR:**
      ($CDCl_3$) δ 10.55 (b s, 1H), 7.76 (dd, *J* = 4.8, 8.3, 1H), 7.31 (app t, *J* = 2.7,

1H), 6.83 (dd, J = 8.4, 9.6, 1H), 6.67 (app t, J = 2.9, 1H), 2.68 (s, 3H); **HPLC**
R_t = 1.343.

Intermediate 28

Intermediate 28
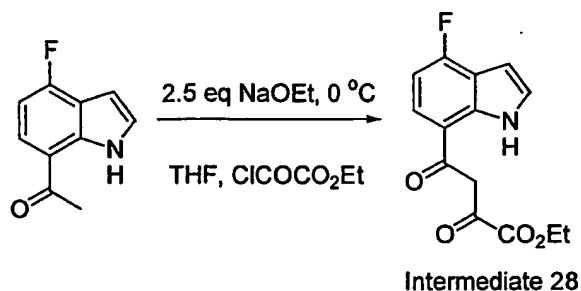
To the 7-acetyl-4-fluoroindole (500 mg, 2.82 mmol) in dry THF (10 ml) was added NaOEt (2.3 ml, 7.06 mmol, 21% w/w in EtOH) dropwise over 10 min at 0°C, and the resulting mixture stirred for 1 hr. Ethyl chlorooxoacetate (424 mg, 3.10 mmol) in dry THF (1 ml) was then added dropwise over 5 min. to the reaction mixture. After stirring for another 3 hr at 0°C, the reaction was quenched with 1 N hydrochloric acid to pH ~4, and added CH$_2$Cl$_2$ (50 ml). The organic layer was separated, washed with H$_2$O (30 ml) and brine (30 ml), dried (MgSO$_4$), and evaporated *in vacuo*. The residue was purified by flash chromatography (30 to 50% EtOAc/Hexane) to give the α,γ-diketoester (464 mg, 59%) as yellow solids. **^{1}H NMR** (CDCl$_3$, indicated an enol form) δ 10.50 (b s, 1H), 7.84 (dd, J = 4.8, 8.5, 1H), 7.34 (appt, J = 2.7, 1H), 7.2 (s, 1H), 6.88 (dd, J = 8.5, 9.5,1H), 6.70 (dd, J = 2.4, 3.2,, 1H), 4.42 (q, J = 7.2, 2H), 1.43 (t, J = 7.2, 3H); **HPLC** R_t = 1.393.

Intermediate 29

Intermediate 29

97
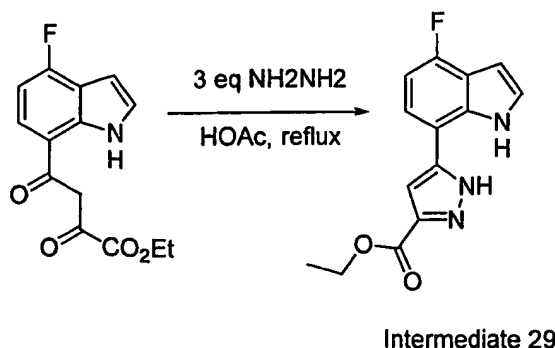
An oven dried 15 ml flask was charged with the α,γ-diketoester **intermediate 28** (180 mg, 0.650 mmol) and HOAc (5 ml), followed by anhydrous hydrazine (61 μl, 1.95 mmol) at r.t. The mixture was then refluxed at 140°C under N_2 for 3 hr. After cooling to r.t., the volatile was evaporated *in vacuo*. The
5   residue was dissolved in CH_2Cl_2 (50 ml), and the resulting solution washed with H_2O (2 x 30 ml) and dried ($MgSO_4$). After evaporation *in vacuo*, the yellow solid residue was triturated with ether (2 x 0.5 ml) and dried under high vacuum to afford the ethyl pyrrazole-3-carboxylate (110 mg, 62%) as yellow solids. **¹H NMR** ($CDCl_3$) δ 10.33 (b s, 1H), 7.46 (dd, *J* = 4.7, 8.1, 1H),
10   7.31 (app t, *J* = 2.7, 1 H), 6.84 (dd, *J* = 8.1, 9.9, 1H), 6.68 (dd, *J* = 2.4, 3.2, 1H), 4.45 (q, *J* = 7.1, 2H), 1.44 (t, *J* = 7.2, 3H); **LC/MS:** (ES+) m/z (M+H)⁺ = 274, HPLC R_t = 1.717.

Intermediate 30

15
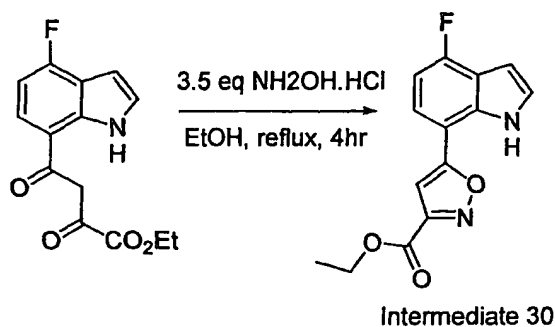
Intermediate 30

An oven dried 50 ml flask was charged with the α,γ-diketoester **intermediate 28** (437 mg, 1.58 mmol) and absolute ethanol (20 ml) to give a suspension,
20   which at rt was added hydroxyamine hydrochloride (387 mg, 5.52 mmol). The reaction mixture was refluxed at 85°C for 4 h, then cooled to rt and evaporated *in vacuo*. The solution of the residue in CH_2Cl_2 (100 ml) was washed with H_2O (2 x 20 ml) and brine (20 ml), and dried (MgSO4). After evaporation *in vacuo*, the solids obtained were triturated with dry ether (2 x 1
25   ml) to give the ethyl isoxazole-3-carboxylate as a light yellow solid (384 mg, 89%). **¹H NMR** (CDCl3), δ 9.47 (b s, 1H), 7.51 (dd, *J* = 4.8, 8.3, 1H), 7.36 (app t, *J* = 2.8, 1H), 6.97 (s, 1H), 6.90 (dd, *J* = 8.4, 9. 5, 1H), 6.74 (dd, *J* = 2.3, 3.1, 1H), 4.5 (q, *J* = 7.1, 2H), 1.47 (t, *J* = 7.1, 3H); **LC/MS:** (ES+) m/z

$(M+H)^+ = 275$, HPLC (0.2% H_3PO_4 buffer, gradient time = 4 min, flow rate = 2 ml/min) R_t = 4.60.
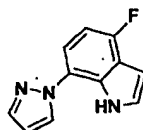
INTERMEDIATE 31

Intermediate 31 was prepared by heating a mixture of intermediate 1 (1.0 g, 4.67 mmol), pyrazole (636 mg, 9.34 mmol), Cs_2CO_3 (3.04 g, 9.33 mmol) and CuBr (134 mg, 0.934 mmol) in $PhNO_2$ (2.0 ml) in a reusable sealed tube at 140°C for 20 h. The crude product was used without further purification. ^1H **NMR:** $(CDCl_3)$ δ 10.46 (b s, 1H), 8.06 (d, $J = 2.6$, 1H), 7.78 (d, $J = 1.7$, 1H), 7.30 (t, $J = 2.7$, 1H), 7.18 (dd, $J = 8.4, 3.9$, 1H), 6.80 (app t, 1H), 6.68 (t, $J = 2.7$, 1H), 6.51 (t, $J = 2.0$, 1H); **LC/MS:** (ES+) m/z $(M+H)^+ = 202$, HPLC R_t = 1.437.

INTERMEDIATE 32
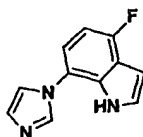
Intermediate 32 was prepared in the same manner as intermediate 31. The crude product was used without further purification. **LC/MS:** (ES+) m/z $(M+H)^+ = 202$, HPLC R_t = 0.893.
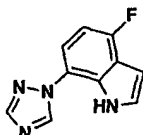
INTERMEDIATE 33

Intermediate 33 was prepared in the same manner as intermediate 31. The crude product was purified by preparative TLC (5% $MeOH/CH_2Cl_2$, 500 μm x 20 cm x 20 cm plates). The position of indole ring at the triazole N1 was

supported by NOE studies. ^{1}H NMR: (CD$_3$OD) δ 9.07 (s, 1H), 8.28 (s, 1H), 7.43 (dd, J = 8.5, 4.0, 1H), 7.37 (d, J = 3.2, 1H), 6.84 (dd, J = 9.6, 8.5, 1H), 6.64 (d, J = 3.2, 1H); LC/MS: (ES+) m/z (M+H)$^+$ = 203, HPLC R$_t$ = 1.223.

5 <u>INTERMEDIATE 34a, b, c</u>
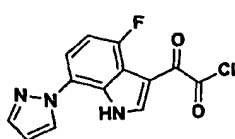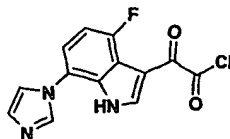
Intermediate 34a   34b   34c
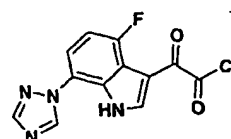
Intermediate 34a, b, and c were prepared in the same manner as
10 intermediate 26.
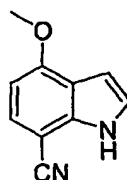
<u>INTERMEDIATE 35</u>

15
To an oven dried 500 ml round bottom flask at rt. was charged with 4-methoxy-7-bromo-indole intermediate 5 (12.8 g, 56.6 mmol) and dry DMF (120 ml), followed by CuCN (25.3 g, 283 mmol). The reaction mixture was refluxed at 165 °C for 16 hr. After cooling to rt., the mixture was slowly
20 added ammonium hydroxide (100 ml), stirred for 10 min, concentrated *in vacuo* to ~50 ml and diluted with CHCl$_3$ (250 ml). The organic mixture was washed with H$_2$O (250 ml), and the aqueous layer back extracted with CHCl$_3$ (2 x 200 ml). The combined organic extracts were filtered through a filter paper to remove some solids, and washed again with H$_2$O (100 ml) and brine
25 (100 ml), and then dried (MgSO$_4$). After evaporation *in vacuo*, the residue was purified by flash column chromatography (10% EtOAc/Hexane (250 ml), then 25% EtOAc/Hexanes (1250 ml)) to afford 4-methoxy-7-cyanoindole intermediate 35 (8.0 g, 82%) as yellow solids. ^{1}H NMR: (CDCl$_3$) δ 8.73 (b s, 1H), 7.50 (d, J = 8.3 Hz), 7.22 (app t, J = 2.8 Hz, 1H), 6.73 (dd, J = 2.3, 3.2
30 Hz, 1H), 6.58 (d, J = 8.3 Hz, 1H), 4.01 (s, 3H); LC/MS: (ES+) m/z (M+H)$^+$ =

173, HPLC (YMC C18 S7 3 x 50 mm, Flow Rate 4 ml/min, Gradient Time 3 min) R_t = 1.700.

INTERMEDIATE 36

5
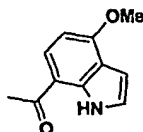
Intermediate 36 was prepared in the same manner as intermediate 27. The crude product was used without further purification. **^{1}H NMR:** (CDCl$_3$) δ 10.48
10 (b s, 1H), 7.77 (d, J = 8.4, 1H), 7.22 (app t, 1H), 6.67 (dd, J = 3.1, 2.4, 1H), 6.56 (d, J = 8.4, 1H), 4.04 (s, 3H), 2.65 (s, 3H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 190, HPLC R_t = 1.277.

INTERMEDIATE 37

15
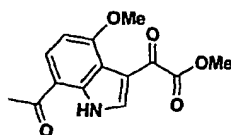
A mixture of intermediate 36 (153.3 mg, 0.81 mmol) and AlCl$_3$ (864.0 mg, 6.48 mmol) in CH$_2$Cl$_2$ (3.0 ml) was stirred at 0°C for 2 h before adding methyl
20 chlorooxoacetate (0.9 ml, 9.79 mmol). The mixture was stirred at 0°C for 2 h, left standing in a freezer for 15 h and then stirred at 0°C again for 5 h. After which time, the mixture was carefully added water (~10 ml) and extracted with EtOAc (30 ml). The organic extract was evaporated in *vacuo* and purified by flash chromatography (2% to 5% MeOH/ CH$_2$Cl$_2$) to give
25 intermediate 37. **^{1}H NMR:** (CD$_3$OD) δ 8.12 (s, 1H), 8.01 (d, J = 8.5, 1H), 6.86 (d, J = 8.5, 1H), 4.00 (s, 3H), 3.91 (s, 3H), 2.64 (s, 3H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 276, HPLC R_t = 1.140.

INTERMEDIATE 38
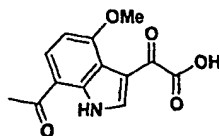
5   Intermediate 37 (30.0 mg, 0.109 mmol) was hydrolysed using NaOH (1 *N*, aq.) in MeOH. After reaction, the mixture was concentrated, and the residue obtained dissolved in water and acidified with HCl (1 *N*, aq.). The aqueous mixture was filtered and the filtrate evaporated to give intermediate 38, which was used without further purification. **LC/MS:** (ES+) m/z (M+H)$^+$ = 262, HPLC
10   R$_t$ = 0.833.

INTERMEDIATE 39
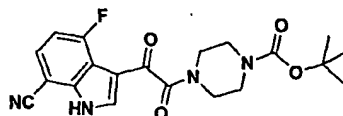
15

Intermediate 39 was prepared analogously to intermediate 12 by coupling intermediate 11 with 1-tert-butyl piperazinecarboxylate, and purified by preparative TLC (60% EtOAc/Hexane, 500 μm x 20 cm x 20 cm plates).
¹H NMR: (CDCl$_3$) δ 9.68, (b s, 1H), 8.19 (d, *J* = 3, 1H), 7.64 (dd, *J* = 8.4, 4.2,
20   1H), 7.08 (dd, *J* = 10.0, 8.4, 1H), 3.74 (app t, 2H), 3.57 (app t, 2H), 3.51 (b s, 4H), 1.48 (s, 9H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 401, HPLC R$_t$ = 1.453.
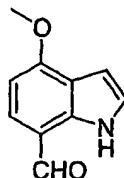
INTERMEDIATE 40

25

To an oven dried 250 ml round bottom flask was charged 7-bromo-4-methoxyindole intermediate 5 (5.0 g, 22.2 mmol) and dry THF (100 ml) at rt. The mixture was cooled to − 78°C, and added ^{n}BuLi (26.7 ml, 66.7 mmol, 2.5

M in hexanes) dropwise *via* a syringe over 30 min. After 10 min., the mixture was warmed to 0°C and stirred for 30 min. The mixture was then cooled to –78°C, and added anhydrous DMF (8.6 ml, 111 mmol) dropwise over 5 min. After 10 min., the mixture was warmed gradually to rt. and stirred for 2 hr.

5   The reaction was then quenched by adding H_2O (100 ml) and the mixture extracted with Et_2O (3 x 100 ml). The combined organic extracts were washed with brine (100 ml) and dried ($MgSO_4$). After evaporation *in vacuo*, the residue was purified by flash column chromatography (EtOAc/hexane) to afford the aldehyde 40 (3.7 g, 95%) as a white solid. **¹H NMR:** (300 MHz,

10    $CDCl_3$) δ 10.15 (b s, 1H), 9.96 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.21 – 7.26 (m, 1H), 6.67 – 6.72 (m, 1H), 6.66 (d, *J* = 8.4 Hz, 1 H), 4.06 (s, 3H); **LC/MS:** (ES+) m/z $(M+H)^+$ = 176, HPLC (YMC C18 S7 3 x 50 mm, Flow Rate 4 ml/min, Gradient Time 2 min) R_t = 1.196.

15   **INTERMEDIATE 41**
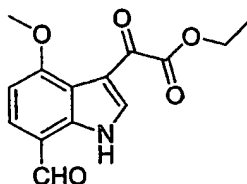
To an oven dried 100 ml round bottom flask was charged with the aldehyde

20   40 (1.78 g, 10.2 mmol) and anhydrous CH_2Cl_2 (60 ml) to give a solution, which was cooled to 0°C, and added $AlCl_3$ (2.72 g, 20.3 mmol) portionwise. The color of the reaction mixture turned purple immediately and was stirred at 0°C for 3 hr. Ethyl chlorooxoacetate (2.77g, 2.27 ml, 20.3 mmol) was then added dropwise to the mixture *via* a syringe. After stirring for 1 hr, the

25   reaction mixture was warmed to rt., and stirred overnight. The reaction was then quenched with hydrochloric acid (30 ml, 1 *N*), H_2O (100 ml), and the resulting mixture extracted with $CHCl_3$ (3 x 100 ml). The combined organic extracts were washed with H_2O (100 ml), brine (100 ml) and dried ($MgSO_4$). After evaporation *in vacuo*, the residue was purified by flash column

30   chromatography (30~50% EtOAc/hexane) to give the expected intermediate 41 (1.3 g, 46%). **¹H NMR:** ($CDCl_3$) δ 10.76 (b s, 1H), 9.97 (s, 1H), 8.18 (d, *J* = 3 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), (4.40 (q, *J* = 7.2 Hz, 2H), 4.03 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H); **LC/MS:** (ES+) m/z $(M+H)^+$

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= 276, HPLC (YMC C18 S7 3 x 50 mm, Flow Rate 4 ml/min, Gradient Time 2 min) R_t = 1.200.

INTERMEDIATE 42

5
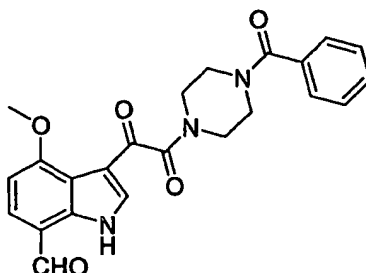
To the ethyl ester intermediate 41 (1.3 g, 4.73 mmol) in MeOH (50 ml) at rt. was added aqueous NaOH (2 ml, 10 mmol, 5 N), and the mixture stirred 10 overnight. After removing part of the solvent *in vacuo*, the residue was acidified with concentrated hydrochloric acid to pH ~2 to form a white solid. The solid was filtered, washed with H_2O (2 ml) and dried to give 1.4 g of the acid, which was used directly in the coupling reaction without further purification. To the acid in DMF (50 ml) was added benzoylpiperazine 15 hydrochloride (1.18g, 5.20 mmol), N,N-diisopropylethylamine (3.06 g, 4.1 ml, 23.7 mmol) and 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazo-4(3H)-one (1.56 g, 5.20 mmol). The reaction mixture was stirred at rt. overnight. After removing part of the solvent *in vacuo*, the residue was dissolved in CH_2Cl_2 (200 ml), and washed with $NaHCO_3$ (100ml, *sat. aq.*), H_2O (100ml), brine 20 (100ml), and dried ($MgSO_4$). After evaporation *in vacuo*, the crude compound was purified by flash column chromatography to give the desired intermediate 42 (1.64 g, 83% two steps). **¹H NMR:** ($CDCl_3$) δ 10.8 (b s, 1H), 9.98 (s,1H), 8.09 (s, IH), 7.73 (d, J = 8.0 Hz, 1H), 7.56-7.32 (b, 5H), 6.82 (d, J = 8.1 Hz, 1H), 4.06 (s, 3H), 3.32-4.2 (m, 8H); **LC/MS:** (ES+) m/z (M+H)⁺ = 25 420, HPLC (YMC C18 S7 3 x 50 mm, Flow Rate 4 ml/min, Gradient Time 2 min) R_t = 1.213.

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INTERMEDIATE 43

COOH
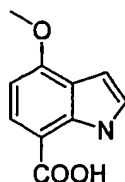
5   A mixture of 4-methoxy-7-cyanoindole (intermediate 35) in EtOH (20 ml) was
added to a solution of KOH (2.45 g, 43.8 mmol) in H_2O (2 ml) at rt., and the
reaction mixture refluxed overnight. After cooling to rt., the solvent was
partially removed *in vacuo*, and the residue acidified with 10% hydrochloric
acid to pH ~2. The resulting white precipitates weres filtered and washed
10   with CH_2Cl_2 (4 x 10 ml). The combined organic washings were washed with
H_2O (10 ml), dried ($MgSO_4$) and evaporated *in vacuo* to afford 2.1 g of the
crude acid, which was used in the next step without further purification.
LC/MS: (ES+) m/z $(M+H)^+$ = 192, HPLC (YMC C18 S7 3 x 50 mm, Flow Rate
4 ml/min, Gradient Time 2 min) R_t = 1.217.

15

INTERMEDIATE 44
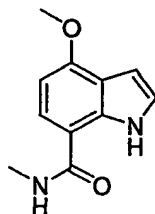
20   To a mixture of the acid intermediate 43 (179.3 mg, 0.94 mmol) in
MeOH/PhH (6 ml, 50:50) at rt. was added $TMSCHN_2$ (4 ml, ~2 *M* in hexane)
dropwise, and the mixture stirred for 1 hr. The solvent and excess reagent
were removed *in vacuo*, and the residue dissolved in MeOH and then purified
by reverse phase preparative HPLC to give the methyl ester (165.2 mg,
25   86%); ¹H NMR: (the methyl ester CDCl₃) δ 9.85 (b s, 1H) 7.87 (d, *J* = 8.4 Hz,
1H), 7.21 (t, *J* = 2.7 Hz, 1H), 6.68 (t, *J* = 2.8 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H),
4.02 (s, 3H), 3.96 (s, 3H). The methyl ester was treated with CH_3NH_2 (4 ml,
40% in H_2O) and stirred at rt. overnight. After removing the excess reagent
in vacuo, the residue was purified by reverse phase preparative HPLC to
30   afford the methylamide (134.8 mg, 82%); LC/MS (the methylamide): (ES+)

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m/z $(M+H)^+$ = 205, HPLC (YMC C18 S7 3 x 50 mm, Flow Rate 4 ml/min, Gradient Time 2 min) R_t = 1.400.

INTERMEDIATE 45

5
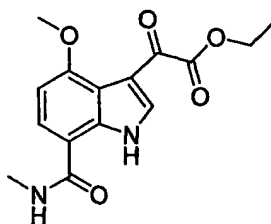
To a mixture of the methylamide intermediate 44 (80 mg, 0.392 mmol) in CH_2Cl_2 (10 ml) at 0°C was added $AlCl_3$ (104.5 mg, 0.784 mmol). The reaction
10   mixture stirred for 3 hr at 0°C, added ethyl chlorooxoacetate (88 μl, 0.788 mmol), and then stirred for a further 1 hr at 0°C before warming to rt. and stirred overnight. The mixture was then acidified with 1 N hydrochloric acid to pH <7, followed by usual aqueous work-up (extracted with $CHCl_3$). The color of the combined organic extracts turned purple during removal of the
15   solvent *in vacuo*. The purple residue obtained was purified by flash column chromatography (EtOAc/hexane) to give the expected intermediate 45 (17 mg, 14%) as a gray solid. **^{1}H NMR:** ($CDCl_3$) δ 11.20 (b s, 1H), 11.19 (b s, 1H), 8.18 (d, J = 3.1 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 3.98 (s, 3H), 3.05 (d, J = 3.1 Hz, 3H), 1.39 (t, J
20   = 7.2 Hz, 3H); **LC/MS:** (ES+) m/z $(M+H)^+$ = 305, HPLC (YMC C18 S7 3 x 50 mm, Flow Rate 5 ml/min, Gradient Time 2 min) R_t = 1.180.

INTERMEDIATE 46

25

106
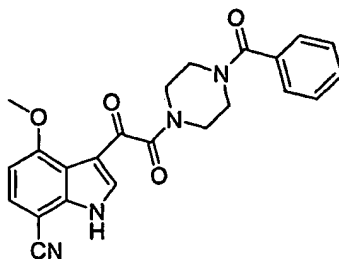
To an oven dried 100 ml round bottom flask was charged with 4-methoxy-7-cyanoindole (0.902 g, 5.24 mmol) and 1,2-dichloroethane (30 ml) at rt. to give a solution. Oxalyl chloride (2.3 ml, 26.2 mmol) was added dropwise and the reaction mixture was refluxed at ~85 °C for 3 hr. After cooling to rt., the

5   solvent and excess reagent were removed *in vacuo*. The residue was dissolved in THF (30 ml), and the mixture added benzoylpiperzine hydrochloride salt (1.43 g, 6.29 mmol) and then stirred for 10 min. The suspension was then cooled to 0 °C, added dropwise *N,N*-diisopropylethylamine (3.39g, 4.6 ml, 26.2 mmol) and stirred for 5 min. After

10   stirring at rt. for 1 hr., the solvent was partially removed *in vacuo*, and the resulting mixture dissolved in MeOH and purified by reverse phase preparative HPLC to afford intermediate 46 as a light yellow solid (1.26 g, 58% two steps). ^{1}H NMR: (CD$_3$OD) δ 8.17 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.47 (b s, 5H), 6.90 (d, J = 8.4 Hz, 1H), 4.00 (s, 3H), 3.44-3.97 (m, 5H);

15   LC/MS: (ES+) m/z (M+H)$^+$ = 417, HPLC (YMC C18 S7 3 x 50 mm, Flow Rate 4 ml/min, Gradient Time 2 min) R$_t$ = 1.220.

INTERMEDIATE 47
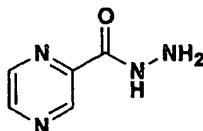
20

A solution of methyl pyrazinecarboxylate (600 mg, 4.34 mmol) in hydrazine (3 ml) was stirred overnight for 20 hours, then at 60°C for 4 hours. Removal of excess hydrazine under high vacuum afforded pyrazine hydrazide

25   intermediate 47 as a yellow solid (550 mg, 92%). ^{1}H NMR: (CD$_3$OD) δ 9.19 (d, J = 1.5, 1H), 8.76 (d, J = 2.4, 1H), 8.65 (app t, 1H); LC/MS: (ES+) m/z (M+H)$^+$ = 139, HPLC R$_t$ = 0.087.

INTERMEDIATE 48

30

Intermediate 48
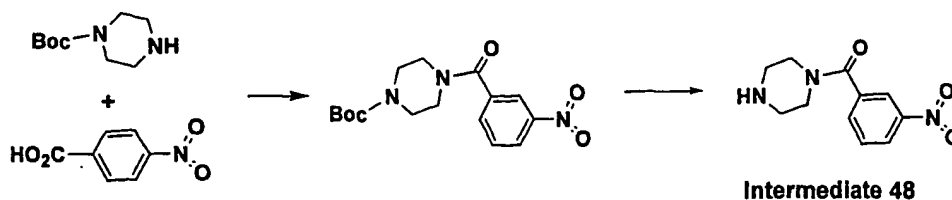
To a mixture of Boc-piperazine (3.678 g, 19.7 mmol) and 4-nitrobenzoic acid (3.0 g, 18 mmol) in CH_2Cl_2 (50 ml) was added DMAP (3.290 g, 26.9 mmol) and EDC (5.146 g, 26.9 mmol). The reaction mixture was stirred at room temperature for 16 hours, and then diluted with CH_2Cl_2 (50 ml). The organic mixture was washed with hydrochloric acid (2 x 100 ml, 1 N, aq.) and water (250 ml), dried ($MgSO_4$), filtered, and then evaporated *in vacuo* to afford the amide intermediate as a white solid (5.80 g, 96%). The amide intermediate was subsequently charged with a solution of hydrogen chloride in dioxane (20 ml, 4 M). The reaction mixture was stirred at room temperature for 4 hours. Removal of the excess reagent under high vacuum afforded Intermediate 48 as a white solid (4.67 g, 99%). ^{1}H NMR (CD_3OD) δ 8.38 (m, 2H), 7.90 (m, 1H), 7.75 (m, 1H), 4.10 – 3.54 (b m, 8H); LC/MS (ES+) m/z $(M+H)^+ = 236$, HPLC $R_t = 0.193$.

INTERMEDIATE 49

Intermediate 49
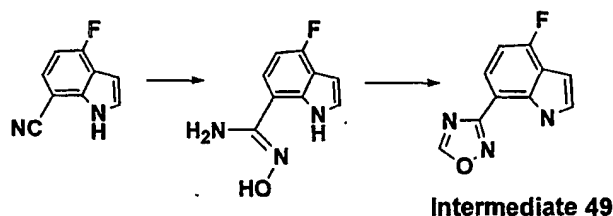
To a mixture of 4-fluoro-7-cyanoindole (reference 102, 1.0 g, 6.24 mmol) in EtOH (50 ml) was added hydroxylamine hydrochloride (651 mg, 9.37 mmol) and triethylamine (1.7 ml). The reaction mixture was refluxed for 16 hours. After removal of the volatile under high vacuum, the residue was added water (10 ml) and filtered to afford the crude hydroxyamindine intermediate. To this intermediate was added triethylorthoformate (10 ml) and the mixture heated at 110°C for 16 hours. After removal of most of the excess reagent, the residue was purified by flash chromatography with (CH_2Cl_2) to give intermediate 49 as pale yellow solid (419 mg, 33%). ^{1}H NMR ($CDCl_3$) δ 9.90 (s, 1H), 8.80 (s, 1H), 8.01 (app dd, J = 8.3, 4.8, 1H), 7.34 (app t, J = 2.8, 1H), 6.93 (app dd, J = 9.8, 8.3, 1H), 6/74 (app dd, J = 3.2, 2.3, 1H); LC/MS (ES+) m/z $(M+H)^+ = 204$, HPLC $R_t = 1.910$.

108
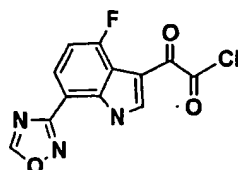
INTERMEDIATE 50

5   To a solution of intermediate 49 (200 mg, 0.984) in CH_2Cl_2 (10 ml) was added oxalyl chloride (1 ml), and the reaction mixture stirred under gentle reflux for 16 hours. Removal of solvent *in vacuo* and the excess reagent under high vacuum afforded intermediate 50 as a yellow solid, which was used without further purification.

10

II. Preparation of Formula I Compounds

EXAMPLE 1
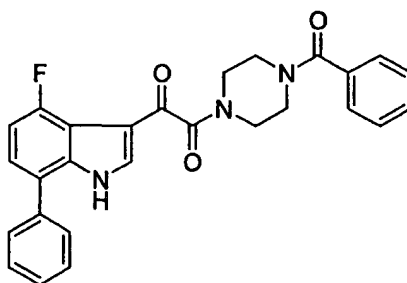
15

     Example of the general procedure for bromide / aryl- or heteroaryl-stannane coupling as described in Schemes 1 and 3:

20   To the 7-bromoindole, intermediate 4, (100 mg, 0.218 mmol) in 3 mL of anhydrous 1,4-dioxane was added 1.2 eq. of tri-n-butylphenyltin (96 mg, 0.262 mmol), and tetrakis(triphenylphosphine)palladium(0) (10 mg, 0.009 mmol). The reaction mixture was heated at 120 °C for 48 h. The reaction mixture was dissolved in EtOAc (10mL) then washed with water (2 x 10 mL), dried (brine,

25    $MgSO_4$) and concentrated in vacuo. The resulting material was purified by SiO_2 flash column chromatography (EtOAc, R_f = 0.2-0.6) using a gradient system (1:1 to 4:1) EtOAc / Hexanes to give a yellow solid. ^{1}H NMR ($CDCl_3$) δ 3.5-3.8 (m, 8 H), 7.05 (dd, 1 H), 7:25 (t, 1 H), 7.35-7.45 (s, 5 H), 7.5-7.6 (m, 4 H), 7.65 (dd, 1 H), 8.02 (d, 1 H), 9.45 (s, 1 H). MS m/e 456.07 (MH$^+$).

EXAMPLE 2
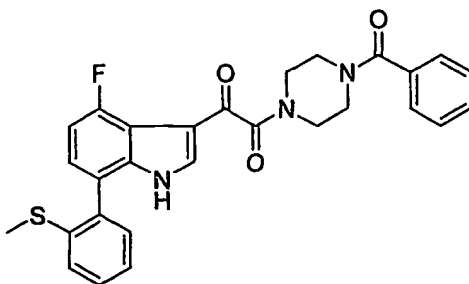
5   The 7- bromoindole, intermediate 4, (100 mg, 0.218 mmol), (2-
      methylthio)phenylboronic acid (44 mg, 0.262 mmol),
      tetrakis(triphenylphosphine) palladium(0) (10 mg, 0.009 mmol), and
      powdered potassium carbonate (60 mg, 0.436 mmol) were dissolved in DMF
      / water (3 mL, 2:1) and placed into a sealed glass reaction tube. The mixture

10   was heated under nitrogen at 120 °C for 48 h. The reaction mixture was
      dissolved in 10 mL EtOAc then washed with 10 mL of water (x2), dried
      (brine, MgSO$_4$) and concentrated in vacuo. The resulting material was
      purified by SiO$_2$ flash column chromatography (EtOAc, R$_f$ = 0.2-0.6) using a
      gradient system (1:1 to 4:1) EtOAc / Hexanes to give a white solid. ^{1}H NMR

15   (CDCl$_3$) δ 2.35 (s, 3H), 3.5-3.8 (m, 8 H), 7.05 (t, 1 H), 7.19 (m, 1 H), 7.27 (d, 2
      H), 7.32 (d, 1 H), 7.35-7.45(m, 6 H), 8.05(s, 1 H), 8.78 (s, 1 H). MS m/e
      502.04 (MH$^+$).

EXAMPLE 3

20
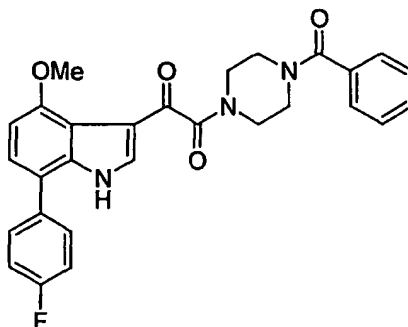
Prepared in the same manner as the compound of Example 2 using
intermediate 6 and 4-Fluorophenyl boronic acid. . ^{1}H NMR (CDCl$_3$) δ 3.5-3.8

(m, 8 H), 3.96 (s, 3 H), 6.77 (d, 1 H), 7.19 (t, 2 H), 7.35-7.45 (s, 5 H), 7.47 (m, 2 H), 7.66 (m, 1 H), 7.98 (s, 1 H), 9.11 (s, 1 H). MS m/e 486.11 (MH$^+$).

EXAMPLE 4

5
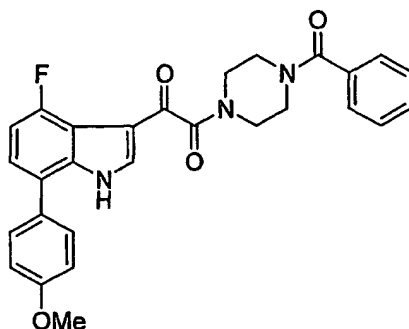
Prepared in the same manner as Example 2 from intermediate 4 and 4-methoxyphenyl boronic acid. ^{1}H NMR (CDCl$_3$) δ 3.5-3.8 (m, 8 H), 3.85 (s, 3

10   H), 7.01 (d, 1 H), 7.03 (d, 2 H), 7.42 (d, 2 H), 7.35-7.45 (s, 5 H), 8.00 (s, 1 H). MS m/e 486.11 (MH$^+$).

EXAMPLE 5

15
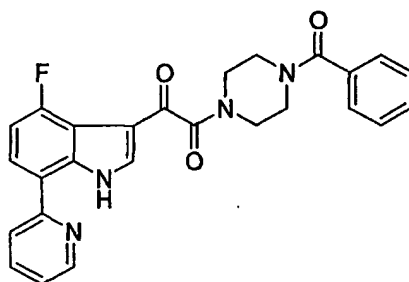
Prepared in the same manner as Example 1 from intermediate 4 and tri-n-butyl(2-pyridinyl)tin. ^{1}H NMR (CDCl$_3$) δ 3.5-3.8 (m, 8 H), 7.05 (t, 1 H), 7.30 (t, 1 H), 7.35-7.45 (s, 5 H), 7.6-8.0 (m, 3 H), 7.65 (dd, 1 H), 8.17 (s, 1 H),

20   8.64 (s, 1 H). MS m/e 457.15 (MH$^+$).

EXAMPLE 6
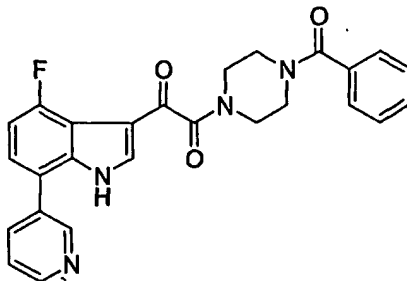
5   Prepared in the same manner as Example 1 from intermediate 4 and
tri-n-butyl(3-pyridinyl)tin. ¹H NMR (CDCl₃) δ 3.5-3.8 (m, 8 H), 7.08 (t, 1 H),
7.22 (m, 1 H), 7.35-7.45 (s, 6 H), 8.05 (t, 1 H), 8.16 (s, 1 H), 8.54 (d, 1 H),
8.80 (s, 1 H), 9.24 (s, 1 H). MS m/e 457.21 (MH⁺).

10   ## EXAMPLE 7
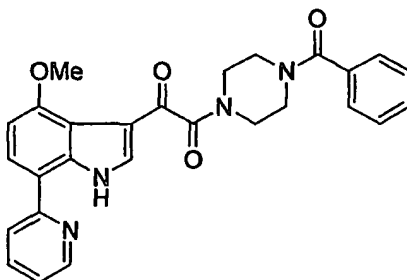
Prepared in the same manner as Example 1 using bromide
15   intermediate 6 and tri-n-butyl(2-pyridinyl)tin. ¹H NMR (CDCl₃) δ 3.5-3.8 (m, 8
H), 4.00 (s, 3 H), 6.78 (d, 1 H), 7.21 (t, 1 H), 7.42 (s, 5 H), 7.78 (d, 1 H), 7.82
(t, 1 H), 7.95 (d, 1 H), 8.11 (s, 1 H), 8.56 (s, 1H). MS m/e 469.19 (MH⁺).

EXAMPLE 8
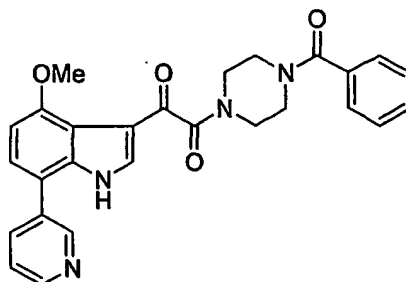
5   Prepared in the same manner as Example 1 using bromide

intermediate 6 and tri-n-butyl(3-pyridinyl)tin. ^{1}H NMR (CDCl$_3$) δ 3.5-3.8 (m, 8

H), 4.06 (s, 3 H), 6.79 (d, 1 H), 7.22 (d, 1 H), 7.35-7.45 (s, 6 H), 7.99 (d, 1 H),

8.05 (s, 1 H), 8.51 (d, 1 H), 8.73 (s, 1 H), 9.18 (s, 1 H). MS m/e 469.25

(MH$^+$).

10

EXAMPLE 9
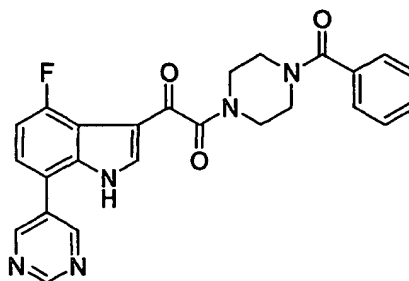
15   Prepared in the same manner as Example 1 using intermediate 4 and

tri-n-butyl (5-pyrimidinyl)tin. ^{1}H NMR (CDCl$_3$) δ 3.5-3.8 (m, 8 H), 7.05 (t, 1 H),

7.33 (dd, 1 H), 7.35-7.45 (s, 5 H), 8.15 (s, 1 H), 9.39 (s, 1 H), 9.54 (s, 2 H),

9.59 (s ,1 H). MS m/e 458.12 (MH$^+$).

113

EXAMPLE 10
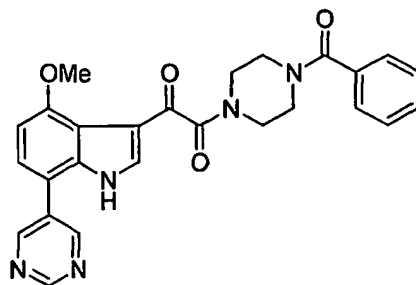
5   Prepared in the same manner as Example 1 using bromide
intermediate 6 and tri-n-butyl (5-pyrimidinyl)tin. ^{1}H NMR (CDCl$_3$) δ 3.5-3.8 (m,
8 H), 7.05 (t, 1 H), 7.33 (dd, 1 H), 7.35-7.45 (s, 5 H), 8.15 (s, 1 H), 9.39 (s, 1
H), 9.54 (s, 2 H), 9.59 (s ,1 H). MS m/e 458.12 (MH$^+$).

10   EXAMPLE 11
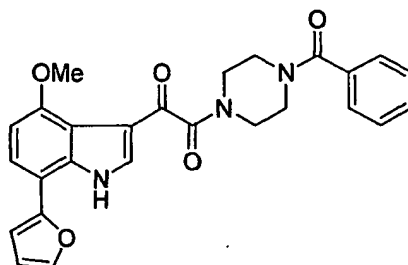
          Prepared in the same manner as Example 2 using bromide
15   intermediate 6 and 2-Furanyl boronic acid. MS m/e 458.06 (MH$^+$), HPLC R$_t$ =
1.427.

EXAMPLE 12

20

114
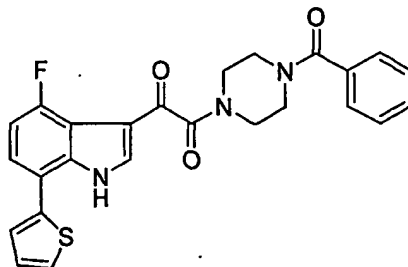
Prepared in the same manner as Example 1 using intermediate 4 and tri-n-butyl (2-thienyl)tin. ^{1}H NMR (CDCl$_3$) δ 3.5-3.(m, 8 H), 7.0 (t, 1 H), 7.15 (t, 1 H), 7.25-7.35 (m, 3 H), 7.35-7.45 (s, 5 H), 8.05 (d, 1 H). MS m/e 462.16 (MH$^+$).
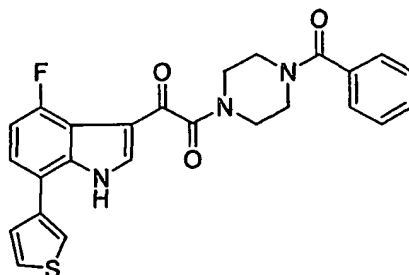
EXAMPLE 13

Prepared in the same manner as Example 2 from intermediate 4 and 3-Thienylboronic acid. ^{1}H NMR (CDCl$_3$) δ 3.5-3.8 (m, 8 H), 7.01 (t, 1 H), 7.24-7.36 (m, 2 H), 7.35-7.65 (m, 7 H), 8.00 (s, 1 H), 9.70 (s, 1 H). MS m/e 462.04 (MH$^+$).
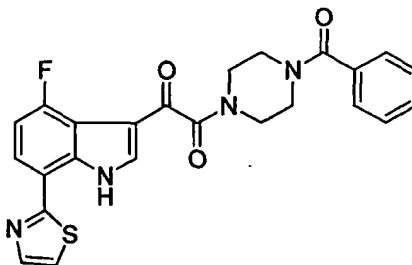
EXAMPLE 14

Prepared in the same manner as Example 2 from intermediate 4 and 2-Thiazolylboronic acid. ^{1}H NMR (CDCl$_3$) δ 3.5-3.8 (m, 8 H), 7.0 (t, 1'H), 7.25 (m, 2 H), 7.35-7.45 (s, 5 H), 8.05 (s, 1 H), 8.15 (s ,1 H), 9.25 (s,1 H). MS m/e 463 (MH$^+$).

115

EXAMPLE 15
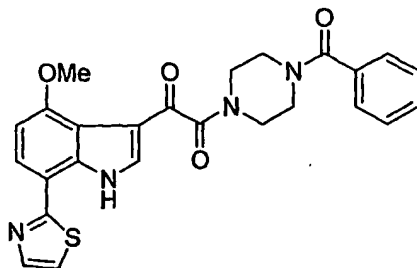
5   Prepared in the same manner as Example 2 using bromide

intermediate 6 and 2-Thiazolyl boronic acid. ^{1}H NMR (CDCl$_3$) δ 3.5-3.8 (m, 8 H), 3.94 (s, 3 H), 6.68 (d, 1 H), 7.23 (d, 1 H), 7.35-7.45 (s, 6 H), 8.08 (s, 1 H), 8.77 (s, 1 H). MS m/e 475.15 (MH$^+$).

10   ## EXAMPLE 16
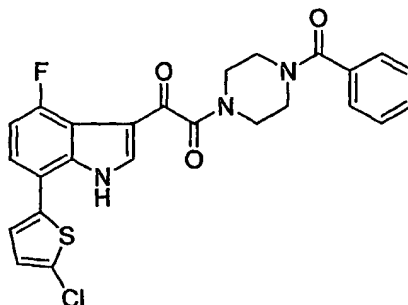
             Prepared in the same manner as Example 2 from intermediate 4 and

15   (5-Chlorothien-2-yl)boronic acid. ^{1}H NMR (CDCl$_3$) δ 3.5-3.8 (m, 8 H), 7.0 (t, 1 H), 7.05 (m, 1 H), 7.28 (t, 1 H), 7.35-7.45 (s, 5 H), 7.53-7.77 (m, 1 H), 8.06 (d, 1 H), 9.68 (s, 1 H). MS m/e 496/497 (MH$^+$).

EXAMPLE 17
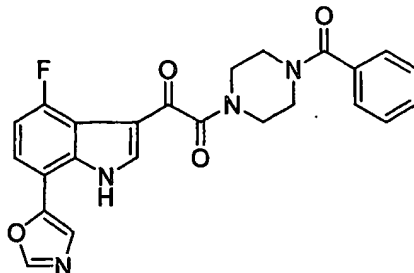
5   The indole carboxaldehyde, intermediate 10, (90 mg, 0.22 mmol),
TOSMIC (43 mg, 0.22 mmol) and powdered K_2CO_3 (31 mg, 0.22 mmol) were
dissolved in MeOH (2 mL) and the solution heated to reflux temperature for 3
h. The MeOH was concentrated in vacuo and the crude material was
dissolved in EtOAc then washed with water (2 x 10 mL), dried (brine, $MgSO_4$)
10   and concentrated in vacuo. The resulting material was purified by SiO_2 flash
column chromatography (95:5) EtOAc / MeOH to give the product as a white
solid (39 mg, 0.09 mmol, 40%). IR (KBr cm^{-1}) 3435(br), 1635, 1433, 1264,
1008, 710. ^{1}H NMR (DMSO-d$_6$) δ 3.5 (m, 4 H), 3.7 (m, 4 H), 7.15 (t, J = 5
Hz, 1 H), 7.45 (m, 5 H), 7.66 (m, 1 H), 7.77 (s, 1 H), 8.18 (s, 1 H), 8.50 (s, 1
15   H). MS m/e 447.15 (MH$^+$). Anal. Calcd for $C_{24}H_{19}FN_4O_4$ • 2.5 H_2O: C, 58.65;
H, 4.92; N, 11.40; Found: C, 58.85; H, 4.29; N, 11.29.

EXAMPLE 18

20
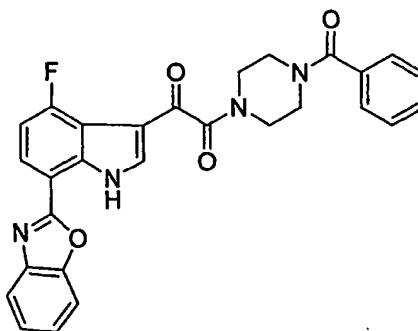
        Prepared in the same manner as Example 1 from intermediate 4 and
tri-n-butyl (2-benzoxazolyl)tin. ^{1}H NMR (CDCl$_3$) δ 3.5-3.8 (m, 8 H), 6.95 (t, 1
H), 7.22 (m, 1 H), 7.35-7.45 (m, 9 H), 8.00 (s, 1 H). MS m/e 497 (MH$^+$).

117
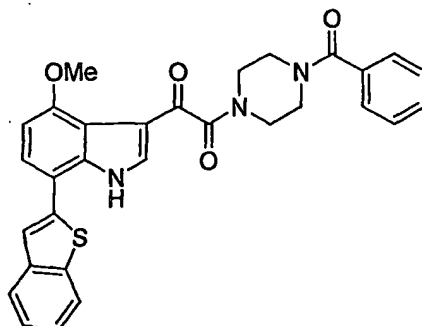
EXAMPLE 19

5   Prepared in the same manner as Example 1 using bromide

intermediate 6 and tri-n-butyl (2-thianapthenyl)tin. ^{1}H NMR (CDCl$_3$) δ 3.5-3.8
(m, 8 H), 4.00 (s, 3 H), 6.78 (d, 1 H), 7.43 (m, 1 H), 7.35-7.55 (m, 7 H), 7.66
(m, 1 H), 7.81 (d, 1 H), 7.87 (d, 1 H), 8.05 (s, 1 H), 9.42 (s, 1 H). MS m/e
524.01 (MH$^+$).

10

EXAMPLE 20
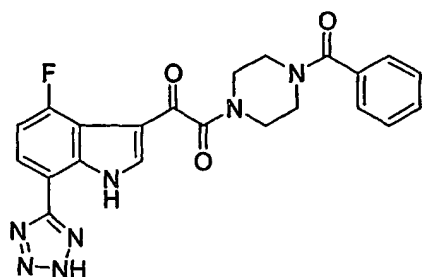
15   A mixture of intermediate 12 (95 mg, 0.23 mmol), NaN$_3$ (47 mg, 0.72
mmol), and NH$_4$Cl (38 mg, 0.71 mmol) in DMF (2 mL) was stirred at 85 °C for
12 h. The reaction mixture was then quenched with HCl (10 drops, 1 N aq.),
diluted with MeOH (2 mL), and subjected to purification by preparative
reverse phase HPLC to afford the tetrazole product as a white solid (61 mg,
20   59%). Separation method: Start %B = 30, Final %B = 100, Gradient time =
10 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 30 x 100mm, Fraction
Collection: 6.16 – 6.68 min. ^{1}H NMR (DMSO) δ 12.52 (s, 1H), 8.18 (s,1H),
7.98 (app dd, J = 8.0, 4.0, 1H), 7.44 (b s, 5H), 7.31 (app t, J = 9.3, 1H), 4.35
– 3.20 (b, m, 8H). LC/MS (ES+) m/z (M+H)$^+$ = 448, HPLC R$_t$ = 1.223.

118
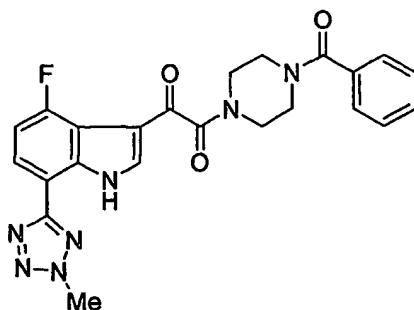
EXAMPLE 21

5   To a suspension of the compound of Example 20 (15 mg, 0.034 mmol) in a mixture of MeOH (0.2 mL)/benzene (0.4 mL) was added (trimethylsilyl)diazomethane (0.04 ml, 0.08 mmol, 2 M in hexane). The resulting mixture was stirred at rt for 90 min., then quenched with excess acetic acid and evaporated *in vacuo*. Purification was performed by
10   preparative reverse phase HPLC using the method: Start %B = 0, Final %B = 85, Gradient time = 12 min, Flow Rate = 30 ml/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 9.05 – 9.42 min. The position of the methyl group at tetrazole N^2 was supported by H-N HMBC. ^{1}H NMR (CDCl$_3$) δ 10.88 (s, 1H), 8.08 (s,1H), 7.94 (app dd, J = 8.3, 4.4, 1H), 7.30 (b s, 5H), 6.98 (app
15   t, J = 9.4, 1H), 4.35 (s, 3H), 3.80 – 3.35 (b, m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 462, HPLC R$_t$ = 1.340.
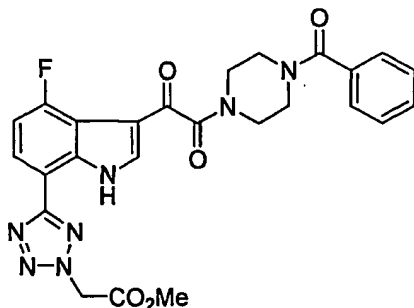
EXAMPLE 22

20

Example of Scheme 20. To a mixture of the tetrazole, intermediate 13, (20 mg, 98.4 μmol) in CH$_3$CN (1 mL) was added methyl bromoacetate (19 μL, 201 μmol) dropwise, followed by K$_2$CO$_3$ (16.3 mg, 118 μmol). The mixture was stirred at rt for 22 h and then evaporated *in vacuo*. The crude

indole residue was then stirred in a solution of oxalyl chloride in CH_2Cl_2 (2.5 mL, 2 M) at rt for 21 h. After evaporation, the crude indole-3-glyoxyl chloride was dissolved in THF (1.0 mL), added excess hydrochloric acid (0.1 mL, 1 N aq. (or pyridine, 50 μl) and stirred at rt for 19 h. The reaction mixture was

5   then diluted with water (10 mL), extracted with EtOAc (40 mL). The organic extract was washed with water (10 mL), dried ($MgSO_4$) and evaporated to give the crude indole-3-glyoxyl acid (36.6 mg). The glyoxyl acid was dissolved in DMF (1 mL) and to it was added intermediate 19 (35.5 mg, 0.157 mmol), DMAP (21.1 mg, 0.173 mmol), EDC (33.3 mg, 0.174 mmol)

10   and NMM (37 μl, 0.337 mmol). The reaction mixture was stirred at rt for 20 h, and then diluted with water to induce precipitation. The precipitates were filtered, washed with hydrochloric acid (2 x 2 mL, 1 N aq.), followed by water, and dried under a stream of air for a short time. The crude material was purified by preparative TLC (EtOAc, 2 x 500 μm x 20 cm x 20 cm plates) to

15   give the product shown above as a colorless glass (8.4 mg, 16% (4 steps from intermediate 13)). ^{1}H NMR ($CDCl_3$) δ 10.95 (b s, 1H), 8.22 (d, J = 2.8, 1H), 8.12 (dd, J = 8.3, 4.3, 1H), 7.43 (b s, 5H), 7.12 (app t, 1H), 5.55 (s, 2H), 4.05 – 3.40 (b m, 8H) 3.87 (s, 3H). LC/MS (ES+) m/z (M+H)$^+$ = 520, HPLC R_t = 1.317.

20

EXAMPLE 23
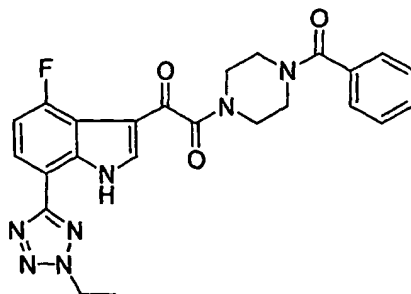
25   Prepared in the same manner as the compound of Example 22. ^{1}H NMR ($CDCl_3$) δ 11.04 (b s, 1H), 8.22 (d, J = 3.1, 1H), 8.10 (dd, J = 8.4, 4.4, 1H), 7.43 (b s, 5H), 7.12 (dd, J = 10.2, 8.4, 1H), 4.79 (q, J = 7.4, 2H), 4.05 – 3.40 (b m, 8H), 1.75 (t, J = 7.4, 3H). LC/MS (ES+) m/z (M+H)$^+$ = 476, HPLC R_t = 1.407.

120
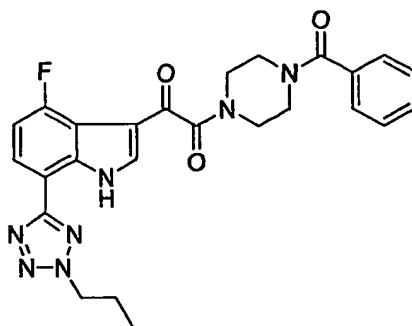
EXAMPLE 24

5   Prepared in the same manner as the compound of Example 22. ^{1}H
NMR (CDCl$_3$) δ 10.52 (b s, 1H), 8.05 (dd, J = 8.3, 4.6, 1H), 7.65 (d, J = 2.5,
1H), 7.45 (b s, 5H), 7.00 (dd, J = 10.2, 8.3, 1H), 4.69 (t, J = 7.1, 2H), 4.05 –
3.35 (b m, 8H), 2.15 (qt, J = 7.4, 7.1, 2H), 1.04 (t, J = 7.4, 3H). LC/MS (ES+)
m/z (M+H)$^+$ = 490, HPLC R$_t$ = 1.530.

10

EXAMPLE 25
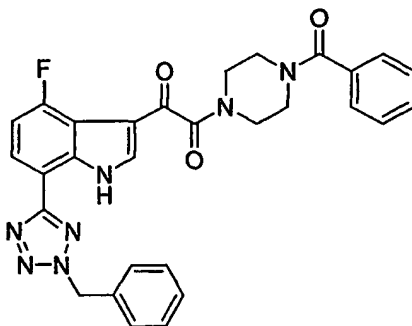
15   Prepared in the same manner as the compound of Example 22. ^{1}H
NMR (CDCl$_3$) δ 10.97 (b s, 1H), 8.20 (b s, 1H), 8.09 (b dd, 1H), 7.44 – 7.40
and (b m, 10H), 7.09 (app t, 1H), 5.87 (s, 2H), 4.00 – 3.35 (b m, 8H). LC/MS
(ES+) m/z (M+H)$^+$ = 538, HPLC R$_t$ = 1.570.

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EXAMPLE 26
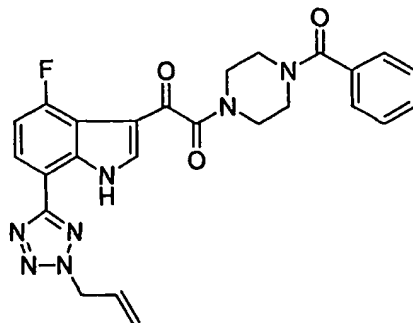
5   Prepared in the same manner as the compound of Example 22. The
position of the allyl group at tetrazole N^2 was supported by H-N HMBC. ^{1}H
NMR (CDCl$_3$) δ 11.00 (b s, 1H), 8.22 (d, J = 3.0, 1H), 8.11 (dd, J = 8.0, 4.5,
1H), 7.43 (b s, 5H), 7.12 (app t, 1H), 6.16 (ddt, J = 16.8, 10.5, 6.3, 1H), 5.48
(d, J = 10.5, 1H), 5.47 (d, J = 16.8, 1H), 5.34 (d, J = 6.3, 1H), 4.00 – 3.35 (b
10   m, 8H). LC/MS (ES+) m/z (M+H)$^+$ = 488, HPLC R$_t$ = 1.443.

EXAMPLE 27
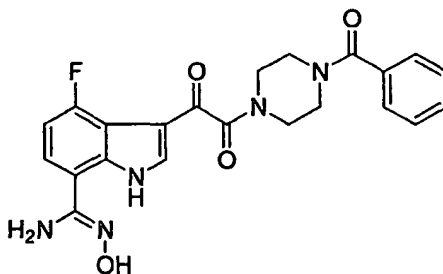
15

To the mixture of intermediate 12 (498 mg, 1.23 mmol) and
hydroxylamine hydrochloride (128 mg, 1.85 mmol) in EtOH (10 mL) was
added triethylamine (0.3 mL, 2.09 mmol). The resulting mixture was stirred at
rt for 36 h. The precipitates were filtered, washed with excess EtOH, and
20   dried under high vacuum to afford the product shown above as a white solid.
The material was used for further transformations without further purification.
^{1}H NMR (DMSO) δ 11.81 (s, 1H), 9.81 (s, 1H), 8.14 (app d, J = 3.5, 1H), 7.66
(app dd, J = 8.5, 4.0, 1H), 7.44 (b s, 5H), 7.08 (app t, J = 9.5, 1H), 6.17 (s,
2H), 3.67 – 3.29 (b m, 8H). LC/MS (ES+) m/z (M+H)$^+$ = 438, HPLC R$_t$ =
25   0.923.

122
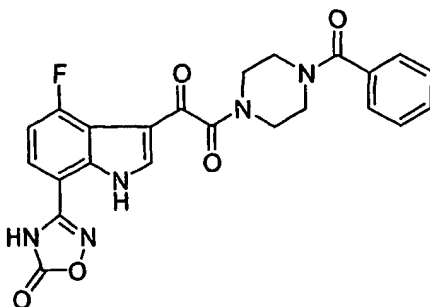
EXAMPLE 28

5   A mixture of the product compound of Example 27 (45 mg, 0.103 mmol) and phosgene (2 mL, 1.04 mmol, 1.92 *M* in toluene) in toluene (3 mL) was heated to reflux for 16 h, and then quenched with excess MeOH (1 mL) and concentrated *in vacuo*. Purification was performed by reverse phase preparative HPLC using the method: Start %B = 30, Final %B = 100,

10   Gradient time = 15 min, Flow Rate = 35 ml/min, Column YMC C18 S5 30 x 100mm, Fraction Collection: 7.78 – 8.30 min. ^{1}H NMR (DMSO) δ 13.23 (s, 1H), 12.26 (s, 1H), 8.13 (app d, *J* = 3.4, 1H), 7.77 (app dd, *J* = 8.3, 4.1, 1H), 7.44 (b s, 5H), 7.30 (app t, *J* = 9.3 1H), 3.80 – 3.30 (b m, 8H). LC/MS (ES+) m/z (M+H)$^+$ = 464, HPLC R$_t$ = 1.220.

15

EXAMPLE 29
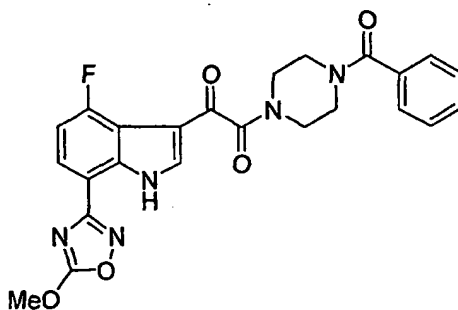
20   To a suspension of the product compound of Example 28 (23 mg, 0.05 mmol) in a mixture of MeOH (0.2 mL)/PhH (0.7 mL) was added (trimethylsilyl)diazomethane (0.05 mL, 0.10 mmol, 2 *M* in hexane). The resulting mixture was stirred at rt for 40 min., quenched with excess acetic acid and evaporated *in vacuo*. Purification was performed by reverse phase

25   preparative HPLC using the method: Start %B = 0, Final %B = 100, Gradient

time = 15 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 10.48 – 11.08 min. The structure was supported by ^{1}H-^{13}C HMBC NMR studies. ^{1}H NMR (CDCl$_3$) δ 10.38 (s, 1H), 8.08 (s, 1H), 7.92 (app dd, J = 8.3, 4.4,1H), 7.33 (b s, 5H), 7.00 (app dd, J = 9.9, 8.7, 1H), 4.24(s, 3H), 3.85 – 3.39 (b m, 8H). LC/MS (ES+) m/z (M+H)$^+$ = 478, HPLC R$_t$ = 1.433.
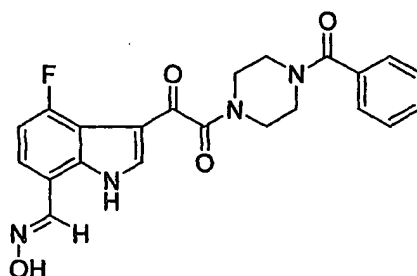
EXAMPLE 30

The indole carboxaldehyde, intermediate 10, (100 mg, 0.25 mmol) and hydroxylamine HCl (21 mg, 0.3 mmol) were suspended in MeOH (2 mL) while NaOMe (0.6 mL, 0.3 mmol, 0.5 M in MeOH) was added dropwise. The mixture was stirred at ambient temperature for 18 h and the volatile solvents removed in vacuo. The resulting gum was triturated with water and extracted into EtOAc. The EtOAc layers were dried (brine, MgSO$_4$) and concentrated in vacuo to give a gum that was triturated with ether. The resulting precipitate was filtered and washed with fresh ether to give the product shown above, (50 mg, 0.12 mmol, 47%). IR (KBr cm^{-1}) 3354(br), 1636, 1514, 1433, 1264, 981, 710. ^{1}H NMR (DMSO-d$_6$) δ 3.4 (m, 4 H), 3.7 (m, 4 H), 7.27 (t, J = 5 Hz, 1 H), 7.45 (m, 5 H), 7.50 (m, 1 H), 8.20 (d, J = 1.8 Hz, 1 H), 8.55 (s, 1 H), 11.39 (s, 1 H), 12.10 (br s, 1H). MS m/e 423.1 (MH$^+$).

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EXAMPLE 31
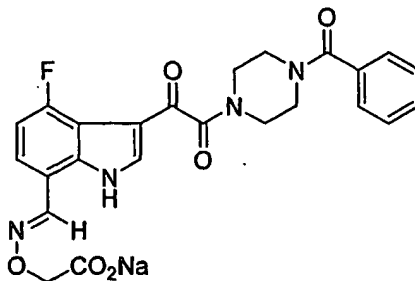
5   The indole carboxaldehyde, intermediate 10, (100 mg, 0.25 mmol) and carboxymethoxylamine HCl (30 mg, 0.14 mmol, MW = 218.59) were suspended in EtOH (2 mL). The mixture was stirred at ambient temperature for 2 h at which time LC/MS indicated the reaction to be 95% done. The mixture was diluted with dry ether and the resulting precipitate was filtered

10   and washed with fresh ether to give the product (compound of formula 37, R_5 = CH_2CO_2H, R_2 = F, $R_{1,3,4,6}$ = H, Scheme 22) (80 mg, 0.17 mmol, 67%). The solid was treated with 0.5 M NaOMe in MeOH until the compound was completely in solution (pH approximately 8) and the volatile components were removed in vacuo to give the product as a sodium salt, shown above.

15   IR (KBr cm^{-1}) 3336 (br), 1628, 1511, 1407, 1266, 927, 710. ^{1}H NMR (DMSO-d_6) δ 3.4 (m, 4 H), 3.7 (m, 4 H), 5.04 (s, 1 H), 7.30 (t, J = 5 Hz, 1 H), 7.60 (m, 5 H), 7.70 (m, 1 H), 8.32 (s, 1 H), 8.83 (s, 1 H), 12.20 (s, 1 H), 13.0 (br s, 1H). MS m/e 481 (MH$^+$).

20   ## EXAMPLE 32
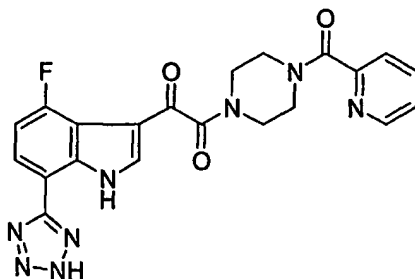
       Prepared in the same manner as the compound of Example 20.

25   Separation method: Start %B = 20, Final %B = 80, Gradient time = 12 min, Flow Rate = 25 mL/min, Column : YMC C18 S5 20 x 100mm, Fraction

125

Collection: 5.27 – 6.74 min. ^{1}H NMR (mixture of conformers, CD$_3$OD) δ 8.66
& 8.58 (app, s & s, 1H), 8.27 (app, d, J = 5.3, 1H), 7.98 (m, 2H), 7.69 (app,
dd, J = 13.3, 8.3, 1H), 7.55 (b m, 1H), 7.19 (m, 1H), 3.98 – 3.57 (b m, 8H);
LC/MS (ES+) m/z (M+H)$^+$ = 449, HPLC R$_t$ = 1.050.

5

EXAMPLE 33
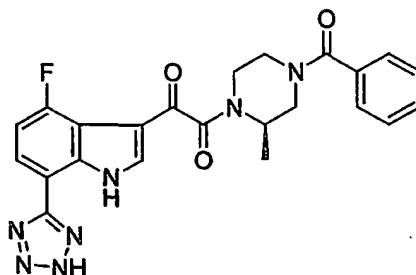
10   Prepared in the same manner as the compound of Example 20.
Separation method: Start %B = 20, Final %B = 100, Gradient time = 12 min,
Flow Rate = 35 ml/min, Column: YMC C18 S5 30 x 100mm, Fraction
Collection: 8.37 – 8.89 min. ^{1}H NMR (mixture of conformers, CD$_3$OD) δ 8.28
and 8.23 (app s, 1H), 7.96 (b s, 1H), 7.46 (b s, 5H), 7.19 (app t, J = 8.4, 1H),
15   4.95 – 3.05 (b m, 7H), 1.40 – 1.26 (b m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 462,
HPLC R$_t$ = 1.247.

EXAMPLE 34
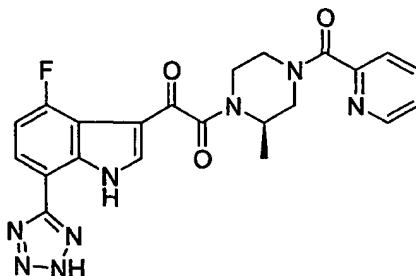
20

        Prepared in the same manner as the compound of Example 20.
Separation method: Start %B = 0, Final %B = 75, Gradient time = 12 min,
Flow Rate = 30 ml/min, Column: YMC C18 S5 20 x 50mm, Fraction
25   Collection: 7.55 – 8.15 min. ^{1}H NMR (CD$_3$OD) δ 8.66 – 8.54 (m, 1H), 8.30 –
8.21 (m, 1H), 8.05 – 7.90 (m, 2H), 7.73 – 7.66 (m, 1H), 7.60 –7.48 (m, 1H),

7.20 – 7.09 (m, 1H), 4.35 – 3.12 (b m, 7H), 1.43 – 1.23 (b m, 3H); LC/MS (ES+) m/z (M+H)+ = 463, HPLC R$_t$ = 1.123.
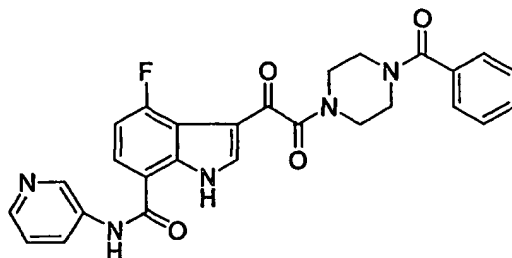
EXAMPLE 35

Example of Method 1:

To a mixture of the acid, intermediate 23, (50 mg, 0.12 mmol)], 3-aminopyridine (45 mg, 0.48 mmol) and DMAP (58 mg, 0.47 mmol) dissolved CH$_2$Cl$_2$ (1 mL) was added EDC (90 mg, 0.47 mmol). The resulting mixture was shaken at rt for 12 h, and then evaporated in vacuo. The residue was dissolved in MeOH, and subjected to preparative reverse phase HPLC purification. Separation method: Start %B = 30, Final %B = 80, Gradient time = 15 min, Flow Rate = 40 mL/min, Column: YMC C18 S5 30 x 100mm, Fraction Collection: 6.57 – 7.02 min. ^{1}H NMR (CD$_3$OD) δ 9.48 (s, 1H), 8.67 (d, J = 8.6, 1H), 8.55 (d, J = 4.8, 1H), 8.22 (s, 1H), 8.06 (dd, J = 8.3, 4.0, 1H), 7.95 (dd, J = 8.5, 5.4, 1H), 7.46 (b, s, 5H), 7.14 (app t, J = 9.2, 1H), 4.00 – 3.45 (b m, 8H); LC/MS (ES+) m/z (M+H)+ = 500, HPLC R$_t$ = 1.130.

EXAMPLE 36

● ●

127
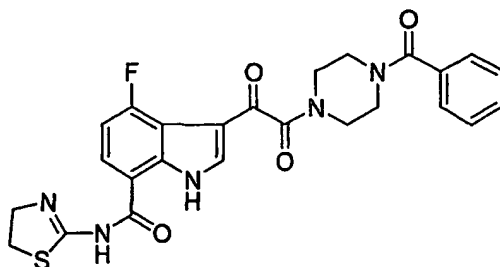
Prepared by Method 1 (as in Example 35) from the acid, intermediate 23, (50 mg, 0.12 mmol)], and 2-amino-2-thiazoline (49 mg, 0.48 mmol). Separation method: Start %B = 20, Final %B = 80, Gradient time = 15 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction

5 Collection: 6.99 – 7.59 min. ^{1}H NMR (CD$_3$OD) δ 8.14 (s, 1H), 8.08 (dd, J = 8.4, 4.5, 1H), 7.42 (b, s, 5H), 7.03 (app t, J = 9.2, 1H), 3.89 (t, J = 8.0, 2H), 3.44 (t, J = 8.0, 2H), 4.00 – 3.45 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 508, HPLC R$_t$ = 1.210.
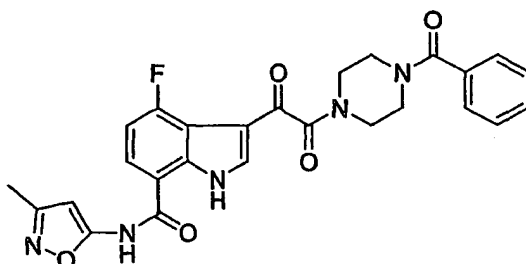
10 **EXAMPLE 37**

Prepared by Method 1 (as in Example 35) from the acid intermediate 23, (50 mg, 0.12 mmol)], and 5-amino-3-methyl isoxazole (49 mg, 0.48 mmol). Separation method: Start %B = 20, Final %B = 80, Gradient time =

15 15 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 9.00 – 9.99 min. ^{1}H NMR (CD$_3$OD) δ 8.20 (s, 1H), 7.99 (dd, J = 8.2, 3.9,1H), 7.46 (b, s, J = 5H), 7.08 (app t, J = 9.3, 1H), 6.46 (s, 1H), 4.00 – 3.45 (b m, 8H), 3.31 (s, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 504, HPLC R$_t$ = 1.380.

20

EXAMPLE 38

128
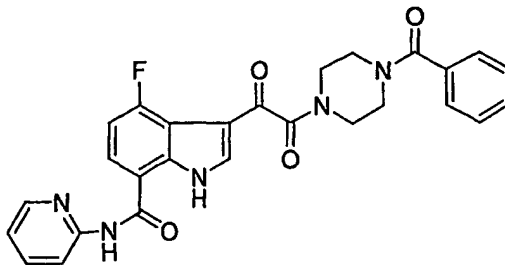
Prepared by Method 1 (as in Example 35) from the acid, intermediate 23, (50 mg, 0.12 mmol)], and 2-aminopyridine (45 mg, 0.48 mmol). Separation method: Start %B = 20, Final %B = 75, Gradient time = 15 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction

5   Collection: 5.72 – 6.33 min. ^{1}H NMR (CD$_3$OD) δ 8.44 (d, J = 3.9, 1H), 8.30 – 8.24 (m, 2H), 8.10 (app t, J = 3.9, 1H), 8.00 (d, J = 8.6, 1H), 7.53 – 7.46 (m, 6H), 7.17 – 7.12 (m, 1H), 4.00 – 3.45 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 500, HPLC R$_t$ = 1.143.

10   **EXAMPLE 39**
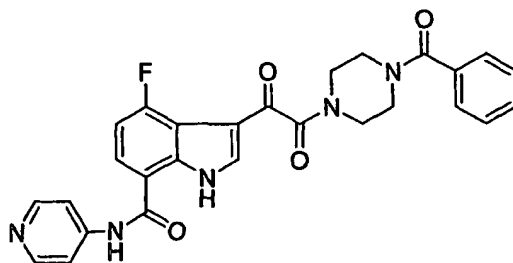
Prepared by Method 1 (as in Example 35) from the acid, intermediate 23, (50 mg, 0.12 mmol)], and 4-aminopyridine (45 mg, 0.48 mmol). Separation method: Start %B = 20, Final %B = 75, Gradient time = 15 min,

15   Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 5.65 – 6.22 min. ^{1}H NMR (CD$_3$OD) δ 8.68 (d, J = 7.2, 2H), 8.43 (d, J = 7.2, 2H), 8.24 (s, 1H), 8.12 (dd, J = 8.3, 4.1, 1H), 7.46 (b s, 5H), 7.17 (app t, J = 9.2, 1H), 4.00 – 3.45 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 500, HPLC R$_t$ = 1.170.

20   **EXAMPLE 40**

129
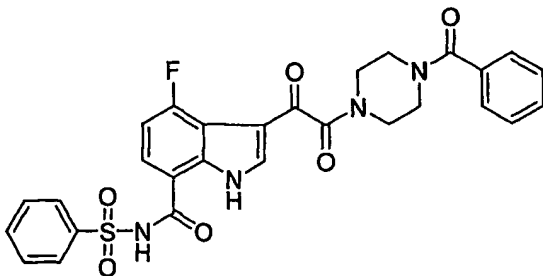
(TFA solvate) Prepared by Method 1 (as in Example 35) from the acid, intermediate 23, (50 mg, 0.12 mmol)], and benzenesulfonamide (75 mg, 0.48 mmol). Separation method: Start %B = 30, Final %B = 90, Gradient time = 15 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 100mm, Fraction

5   Collection: 5.95 – 6.55 min. ^{1}H NMR (CD$_3$OD) δ 8.14 (m, 3H), 7.91 (m, 1H), 7.68 (m, 1H), 7.60 (m, 2H), 7.45 (b m, 5H), 7.07 (app, t, J = 9.4, 1H), 3.82 – 3.44 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 563, HPLC R$_t$ = 1.283.

EXAMPLE 41

10
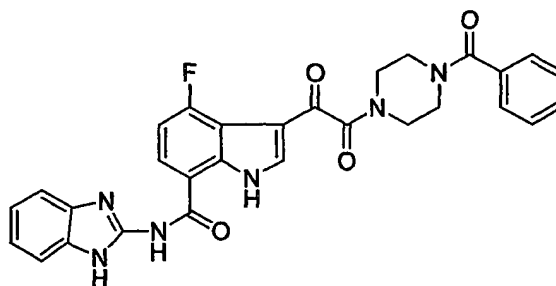
Example of Method 2:

To a mixture of 2-aminobenzimidazole (32 mg, 4 equiv., 0.24 mmol)

15   and HOBT (16 mg, 0.12 mmol) in THF (0.5 mL) was added the acid, intermediate 23, (25 mg, 0.06 mmol)] and NMM (50 µl, 0.45 mmol), followed by EDC (23 mg, 0.12 mmol). The reaction mixture was shaken at rt for 12 h. The volatiles were evaporated in vacuo; and the residue dissolved in MeOH and subjected to preparative reverse phase HPLC purification. Separation

20   method: Start %B = 20, Final %B = 70, Gradient time = 15 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 10.35 – 10.95 min. ^{1}H NMR (CD$_3$OD) δ 8.28 (s, 1H), 8.15 (m,1H), 7.68 (dd, J = 6.0, 3.2, 2H), 7.49 (m, 7H), 7.17 (app t, J = 9.1, 1H), 4.00 – 3.45 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 539, HPLC R$_t$ = 1.323.

130
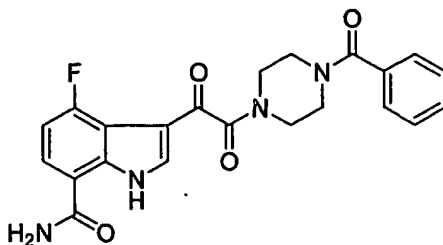
EXAMPLE 42

Prepared according to Method 2 as in Example 41 using excess ammonium chloride as the ammonia equivalent. Separation method: Start %B = 0, Final %B = 75, Gradient time = 12 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 7.41 – 8.00 min. ^{1}H NMR (CD$_3$OD) δ 8.18 (s, 1H), 7.83 (dd, J = 8.1, 4.2, 1H), 7.46 (b, s, 5H), 7.04 (app t, J = 9.1, 1H), 3.95 – 3.40 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 423, HPLC R$_t$ = 1.150.

EXAMPLE 43
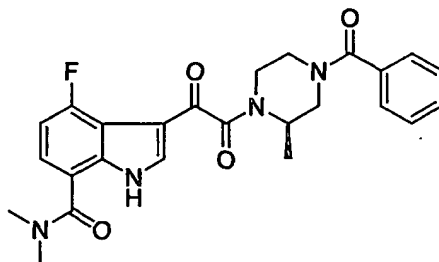
Prepared according to Method 2 as in Example 41 using dimethylamine as the amine component. Separation method: Start %B = 0, Final %B = 80, Gradient time = 12 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 7.63 – 7.92 min. ^{1}H NMR (CD$_3$OD) δ 8.17 (s, 1H), 7.45 (b, s, 5H), 7.34 (dd, J = 7.8, 4.2, 1H), , 7.04 (app t, J = 9.2, 1H), 3.95 – 3.40 (b m, 8H), 3.16 (s, 3H), 3.08 (s, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 451, HPLC R$_t$ = 1.167.

131
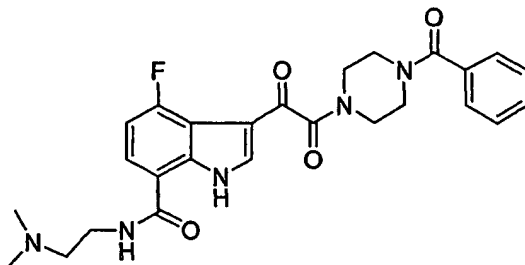
EXAMPLE 44

Prepared according to Method 2 as in Example 41 using N,N-dimethylethylenediamine as the amine component. Separation method: Start %B = 0, Final %B = 75, Gradient time = 15 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 6.82 – 8.05 min. ^{1}H NMR (CD$_3$OD) 8.18 (s, 1H), 7.78 (dd, J = 8.2, 4.1, 1H), 7.45 (b, s, 5H), , 7.04 (app t, J = 9.3, 1H), 3.95 – 3.40 (b m, 8H), 3.81 (t, J = 5.6, 2H), 3.42 (t, J = 5.6, 2H), 3.00 (s, 6H); LC/MS (ES+) m/z (M+H)$^+$ = 494, HPLC R$_t$ = 1.043.
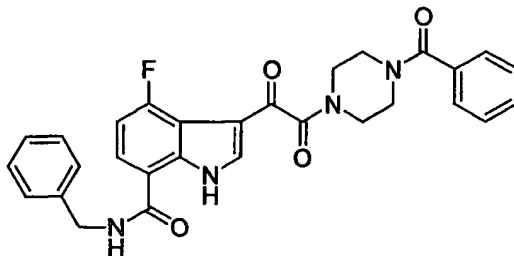
EXAMPLE 45

Prepared according to Method 2 as in Example 41 using benzylamine as the amine component. Separation method: Start %B = 0, Final %B = 90, Gradient time = 15 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 10.95 – 12.18 min. ^{1}H NMR (CD$_3$OD) δ 8.17 (s, 1H), 7.80 (dd, J = 8.2, 4.1, 1H), 7.44 (b, s, 5H), 7.37 (d, J = 7.5, 2H), 7.33 – 7.30 (m, 2H), 7.24 (t, J = 7.3, 1H), 7.03 (app t, J = 9.3, 1H), 4.63 (s, 2H), 3.95 – 3.40 (b m, 8H) LC/MS (ES+) m/z (M+H)$^+$ = 513, HPLC R$_t$ = 1.410.

132
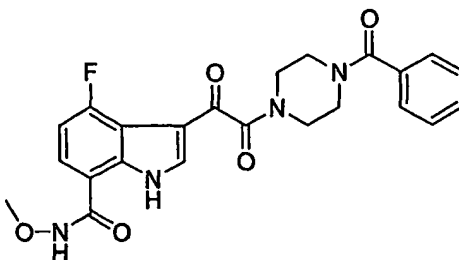
EXAMPLE 46

Example of Method 2. To a solution of acid, intermediate 23, (30.0 mg, 0.071 mmol) in DMF (1 mL) was added methoxylamine hydrochloride (11.8 mg, 0.14 mmol), HOBT (22.9 mg, 0.17 mmol). EDC (32.5 mg, 0.17 mmol), followed by NMM (42 µl, 0.38 mmol). The resulting mixture was stirred at rt for 14 h, and then evaporated *in vacuo*. The residue was treated with water (2 mL) to give precipitates, which were filtered and washed with HCl (2 x 3 mL, ~0.3 N aq.). The precipitates were further washed with water (2 x 2 mL) and dried under high vacuum to give the product shown above as a light pink solid. ^{1}H NMR (CD$_3$OD) δ 8.19 (s, 1H), 7.64 (b dd, 1H), 7.47 (b, s, 5H), 7.03 (b t, J = 9.2, 1H), 4.00 – 3.34 (b m, 8H), 3.85 (s, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 453, HPLC R$_t$ = 1.150.
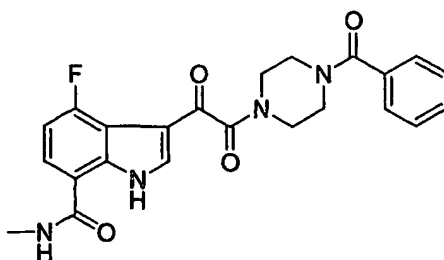
EXAMPLE 47

Prepared according to Method 2 as in Example 41 using methylamine as the amine component. Separation method: Start %B = 0, Final %B = 75, Gradient time = 12 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 7.90 – 8.50 min. ^{1}H NMR (CD$_3$OD) δ 8.17 (s, 1H), 7.71 (dd, J = 8.1, 4.0, 1H), 7.45 (b, s, 5H), 7.01 (app t, J = 9.2, 1H), 3.95 –

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3.40 (b m, 8H), 2.96 (s, 3H); LC/MS (ES+) m/z $(M+H)^+$ = 437, HPLC R_t = 1.123.

Alternatively, the compound of this example can be prepared as
shown and described below.
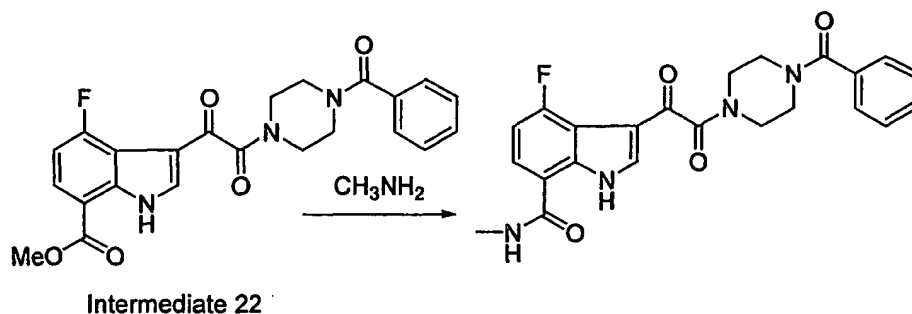
Intermediate 22

To the methyl ester intermediate 22, (60 mg, 0.137 mmol) was added
a solution of methylamine in water (1.5 ml, 18 mmol, 40% aq.) and the
resulting mixture stirred at rt for 52 h. Evaporation of the excess reagent *in vacuo* gave the product as a white solid (58 mg, 97%).

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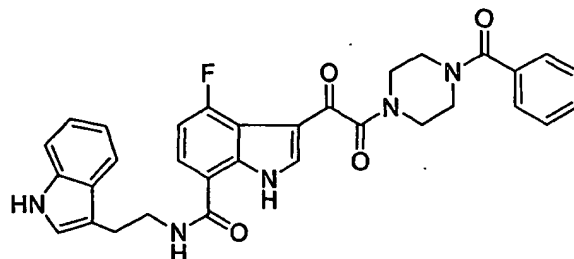
EXAMPLE 48

Prepared according to Method 2 as in Example 41 using 3-(2-
aminoethyl)indole as the amine component. Separation method: Start %B =
0, Final %B = 100, Gradient time = 12 min, Flow Rate = 30 ml/min, Column:
YMC C18 S5 20 x 50mm, Fraction Collection: 8.84 – 9.44 min. ^{1}H NMR
(300M, CD$_3$OD) δ 8.20 (s, 1H), 7.72 – 7.63 (m, 2H), 7.48 (b, s, 5H), 7.40 (d, J
= 7.1, 1H), 7.12 – 6.96 (m, 4H), 3.95 – 3.40 (b m, 8H), 3.74 (t, J = 7.4, 2H),
3.12 (t, J = 7.4, 2H); LC/MS (ES+) m/z (M+H)$^+$ = 566, HPLC R$_t$ = 1.453.

EXAMPLE 49
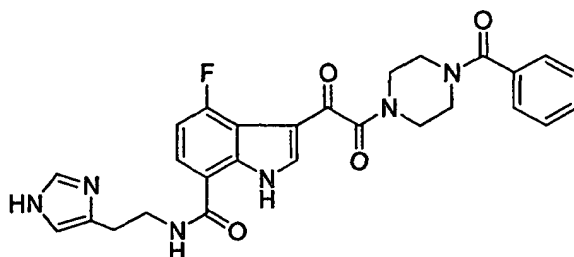
Prepared according to Method 2 as in Example 41 using 4-(2-
aminoethyl)imidazole as the amine component. Separation method: Start
%B = 0, Final %B = 80, Gradient time = 12 min, Flow Rate = 30 mL/min,
Column: YMC C18 S5 20 x 50mm, Fraction Collection: 6.42 – 7.02 min. ^{1}H
NMR (300 MHz, CD$_3$OD) δ 8.82 (s, 1H), 8.19 (s, 1H), 7.73 (dd, J = 8.4, 4.3,
1H), 7.48 (b, s, 5H), 7.39 (s, 1H), 7.04 (dd, J = 10.2, 8.5, 1H), 3.77 (t, J =
6.7, 2H), 3.09 (t, J = 6.7, 2H), 3.95 – 3.40 (b m, 8H); LC/MS (ES+) m/z
(M+H)$^+$ = 517, HPLC R$_t$ = 1.083.

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EXAMPLE 50
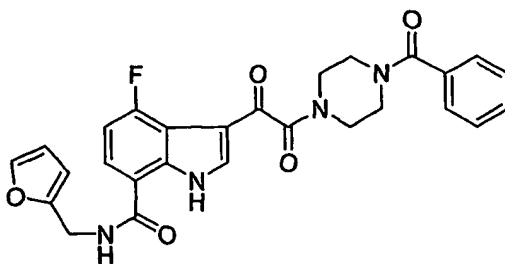
Prepared according to Method 2 as in Example 41 using 2-(aminomethyl)furan as the amine component. Separation method: Start %B = 0, Final %B = 90, Gradient time = 10 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 7.42 – 8.03 min. ^{1}H NMR (CD$_3$OD) δ 8.17 (s, 1H), 7.77(dd, J = 8.1, 4.1,1H), 7.45 (b, s, 5H), 7.42 (s, 1H), 7.01 (app t, J = 9.3, 1H), 6.35 (d, J = 3.1, 1H), 6.31 (d, J = 3.1, 1H), 4.60 (s, 2H), 3.95 – 3.40 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 503, HPLC R$_t$ = 1.283.

EXAMPLE 51
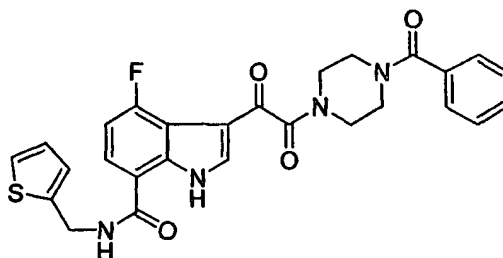
Prepared according to Method 2 as in Example 41 using 2-(aminomethyl)thiophene as the amine component. Separation method: Start %B = 20, Final %B = 90, Gradient time = 12 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 7.21 – 8.43 min. ^{1}H NMR (CD$_3$OD) δ 8.18 (s, 1H), 7.76(dd, J = 7.8, 3.9,1H), 7.45 (b, s, 5H), 7.27 (d, J = 4.7, 1H), 7.06 – 7.00 (m, 2H), 6.94 (dd, J = 5.0, 3.6, 1H), 4.78 (s, 2H), 3.95 – 3.40 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 519, HPLC R$_t$ = 1.347.

EXAMPLE 52
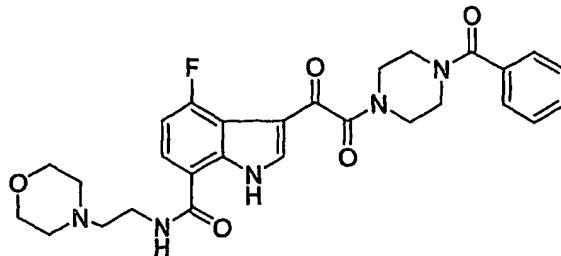
Prepared according to Method 2 as in Example 41 using 4-(2-
aminoethyl)morpholine as the amine component. Separation method: Start
%B = 0, Final %B = 75, Gradient time = 12 min, Flow Rate = 30 ml/min,
Column: YMC C18 S5 20 x 50mm, Fraction Collection: 6.39 – 6.99 min. ^{1}H
NMR (CD$_3$OD) δ 8.18 (s, 1H), 7.78(dd, J = 8.2, 4.0,1H), 7.45 (b s, 5H), 7.04
(app t, J = 9.2, 1H), 4.10 – 3.20 (b overlapping m, 16H), 3.84 (t, J = 5.7, 2H),
3.45 (t, J = 5.7, 2H); LC/MS (ES+) m/z (M+H)$^+$= 536, HPLC R$_t$ = 1.030.

EXAMPLE 53
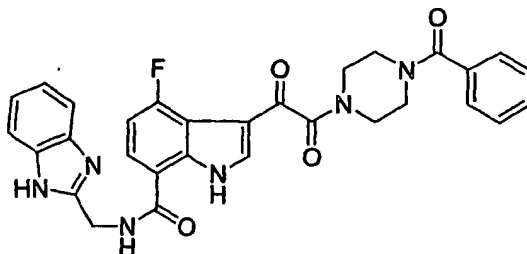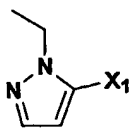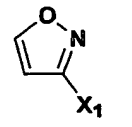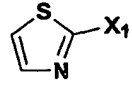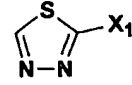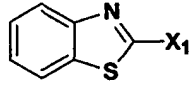
Prepared according to Method 2 as in Example 41 using 2-
(aminomethyl)benzimidazole as the amine component. Separation method:
Start %B = 10, Final %B = 75, Gradient time = 15 min, Flow Rate = 30
mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 7.73 – 8.34
min. ^{1}H NMR (CD$_3$OD) δ 8.14 (s, 1H), 7.93(dd, J = 8.2, 4.5,1H), 7.75 – 7.71
(m, 2H), 7.58 – 7.54 (m, 2H) 7.43 (b, s, 5H), 7.08 (app t, J = 8.7, 1H), 5.08
(s, 2H), 3.95 – 3.40 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 523, HPLC R$_t$ =
1.153.

137
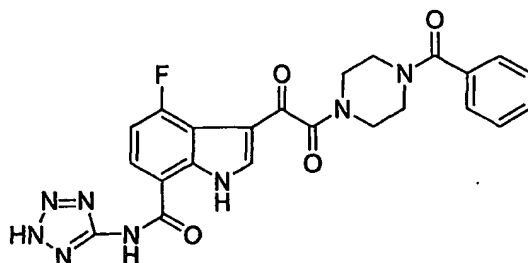
EXAMPLE 54

Example of Method 3:

5   To a mixture of the acid intermediate (compound of **Example 23**), (20 mg, 0.047 mmol) 5-aminotetrazole (4 equiv.) and DEPBT (prepared according to Li, H.; Jiang, X. Ye, Y.; Fan, C.; Todd, R.; Goodman, M. *Organic Letters* **1999**, *1*, 91; 21 mg, 0.071 mmol) in DMF (0.5 mL) was added TEA (0.03 mL, 0.22 mmol). The resulting mixture was shaken at rt for 12 h; and 10   then diluted with MeOH (2 mL) and purified by preparative reverse phase HPLC. Separation method: Start %B = 0, Final %B = 80, Gradient time = 15 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 8.24 – 10.09 min. ^{1}H NMR (CD$_3$OD) δ 8.08 (s, 1H), 7.98 (dd, J = 8.2, 4.0,1H), 7.32 (b, 5H), 7.01 (app t, J = 9.3, 1H), 3.95 – 3.40 (b m, 8H); 15   LC/MS (ES+) m/z (M+H)$^+$ = 491, HPLC R$_t$ = 1.197.

EXAMPLES 55-59

1,1'carbonyldiimidazole
_____
R^{9}NH$_2$, THF, reflux

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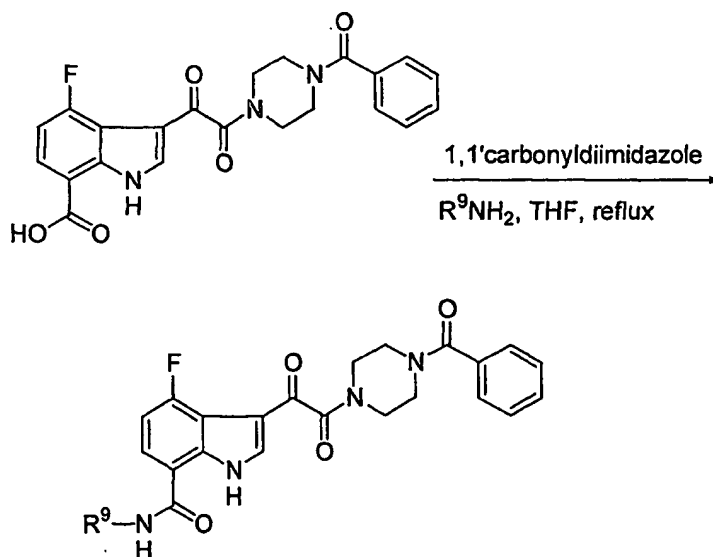
Example of Method 4. The compounds were prepared as follows: A mixture of an acid intermediate (shown above) (0.047mmol) and 8.5 mg (0.052mmol) of 1,1-carbonyldiimidazole in anhydrous THF (2 mL) was heated to reflux under nitrogen. After 2.5h, 0.052 mmol of amine was added and heating continued. After an additional period of 3~20 h at reflux, the reaction mixture was cooled and concentrated in vacuo. The residue was purified by chromatography on silica gel to provide compounds of Formula I in the table below.

R^9 (X$_1$ is point of attachment)	Ex.	HPLC retention time	mass obs. (M+H)+
	55	1.01 min	517
	56	1.02 min	490
	57	1.37 min	506
	58	1.03 min	507
	59	1.77 min	556

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EXAMPLE 60
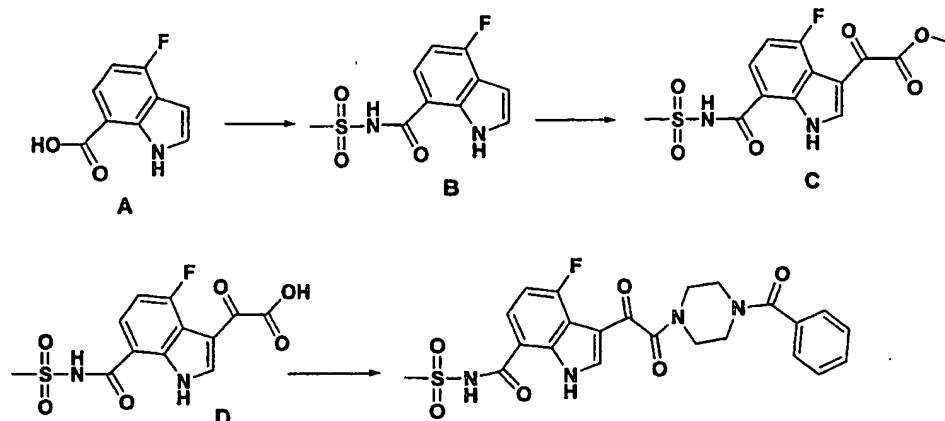
5   To a mixture of A (Reference 102, 50 mg, 0.279 mmol) and methanesulfonamide (32 mg, 0.34 mmol) in CH_2Cl_2 (1 mL), were added DMAP (47 mg, 0.385 mmol) and EDC (64 mg, 0.335 mmol). The resulting mixture was stirred at rt for 17 h. After which time, the mixture was diluted with CH_2Cl_2 (20 mL), washed with hydrochloric acid (3 x 20 mL, 1 N, aq.)
10   followed by water (30 mL), dried ($MgSO_4$) and evaporated *in vacuo* to provide intermediate B as white solid. (66 mg, 92%) ^1H NMR (300 MHz, CD_3OD) δ 7.76 (app, dd, J = 8.4, 4.8, 1H), 7.41 (m,1H), 6.84 (app, dd, J = 9.9, 8.4, 1H), 6.64(m, 1H), 3.44 (s, 3H).

15   To a solution of methyl chlorooxoacetate (0.04 ml, 0.435 mmol) in CH_2Cl_2 (2 mL) was added $AlCl_3$ (52 mg, 0.39 mmol). The resulting suspension was stirred at 4 °C for 20 min. before adding intermediate B (60 mg, 0.234 mmol). After stirring at rt for 15 h, the reaction mixture was quenched with hydrochloric acid (15 mL, ~5 N, aq.) and extracted with EtOAc
20   (3 x 5 mL). The combined organic extracts were washed with water (30 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give intermediate C as a brownish oil. The material was used without further purification.

      To a solution of intermediate C in MeOH (0.5 ml) was added NaOH
25   (0.6 ml, 0.6 mmol, 1 N aq.) and the resulting mixture was stirred at rt for 4.5 h. The mixture was then acidified with hydrochloric acid (1 N, aq.) to pH 3, and the precipitates were filtered. Evaporation of the filtrate under high

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vacuum afforded intermediate D as an off-white solid. The material was used without further purification.

To the solution of intermediate D and intermediate 19 (47 mg, 0.21 mmol) in CH_2Cl_2 was added DMAP (35 mg, 0.286 mmol) and EDC (38 mg, 0.319 mmol). The reaction mixture was stirred at rt for 27.5 h, and then evaporated *in vacuo* to afford a yellow oil, which was purified by preparative reverse phase HPLC using the method: Start %B = 30, Final %B = 100, Gradient time = 8 min, Flow Rate = 40 mL/min, Column: YMC C18 S5 30 x 100mm, Fraction Collection: 4.52 – 4.98 min to provide the final product shown above. ^{1}H NMR (300 MHz, CD_3OD) δ 8.23 (m, 1H), 7.93 (app, dd, J = 8.8, 4.4,1H), 7.48 (b s, 5H), 7.11 (app t, J = 9.7, 1H), 3.90 – 3.40 (b m, 8H), 3.44 (s, 3H); LC/MS (ES+) m/z $(M+H)^+$ = 501, HPLC R_t = 1.143.

EXAMPLE 61
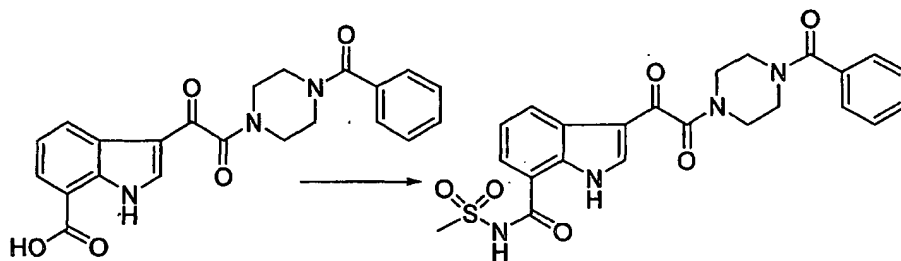
To a suspension of the acid (Reference 102, 30 mg, 0.074 mmol) and methylsulfonamide (0.296 mmol) in CH_2Cl_2 (1 mL), was added DMAP (36 mg, 0.295 mmol) and EDC (56 mg, 0.293 mmol). The resulting mixture was stirred at rt for 16 h, and then evaporated *in vacuo*. The residue was dissolved in MeOH, and subjected to preparative reverse phase HPLC purification to provide the product. Separation method: Start %B = 0, Final %B = 100, Gradient time = 15 min, Flow Rate = 25 mL/min, Column: YMC C18 S5 30 x 100mm, Fraction Collection: 7.83 – 9.15 min. ^{1}H NMR (300 MHz, CD_3OD) δ 8.50 (m, 1H), 8.10 (s, 1H), 7.84 (app, d, J = 6.8, 1H), 7.40 (b m, 6H), 3.90 – 3.40 (b, m, 8H), 3.38 (s, 3H); LC/MS (ES+) m/z $(M+H)^+$ = 483, HPLC R_t = 1.197.

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EXAMPLE 62
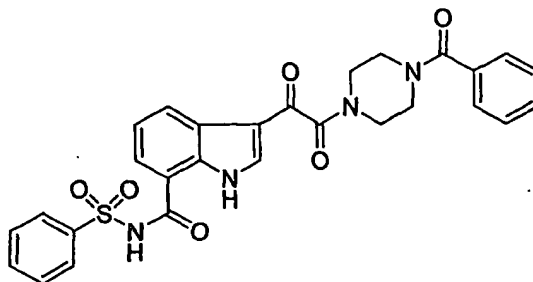
Example of Scheme 25A. Prepared as described above in Example 61 using benzenesulfonamide as the sulfonamide component. Purification 5 was performed by flash chromatography using a gradient elution (100% EtOAc, to 2% to 10% MeOH/EtOAc) to give the product as a white solid. ^{1}H NMR (300 MHz, CD$_3$OD) δ 8.30 (m, 1H), 8.06 – 7.84 (b m, H), 7.53 – 7.18 (b m, 9H), 3.93 – 3.33 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 545, HPLC R$_t$ = 1.387.

10

EXAMPLE 63
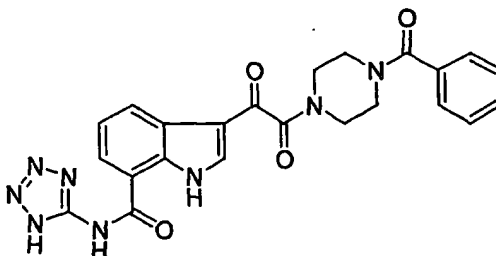
Example of Scheme 25A. Prepared as described above in Example 61 using 3-aminotetrazole as the amine component. Separation method: 15 Start %B = 30, Final %B = 80, Gradient time = 15 min, Flow Rate = 25 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 6.22 – 6.89 min. ^{1}H NMR (300 MHz, CD$_3$OD) δ 8.50 (m, 1H), 8.16 (s,1H), 8.06 (m, 1H), 7.57 – 7.27 (b m, 6H), 3.90 – 3.40 (b, m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 473, HPLC R$_t$ = 1.263.

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EXAMPLE 64
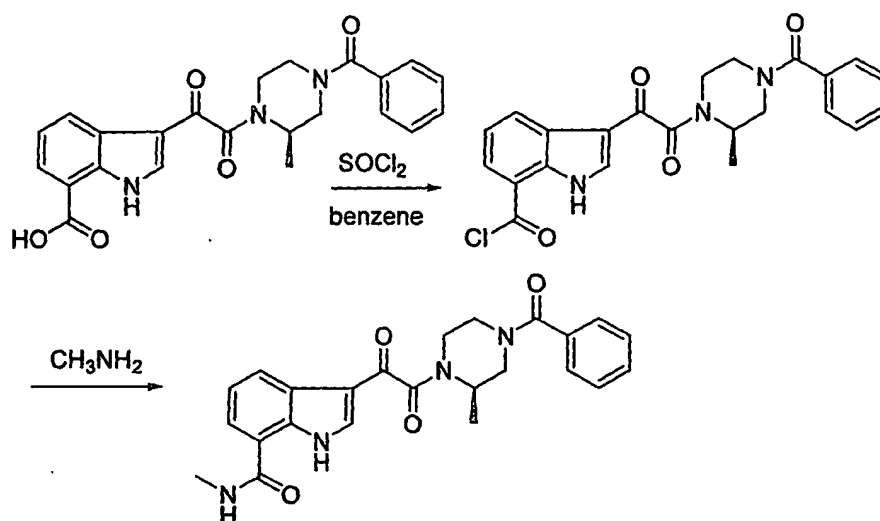
The crude acid chloride was obtained by refluxing a mixture of the
acid shown and excess SOCl$_2$ (1.0 mL per 0.03 mmol of acid) in benzene (15
mL) for 3 h, followed by evaporation of the volatile. A mixture of the acid
chloride (30.0 mg, 0.07 mmol) and excess amine (1.0 mL of a 2 M solution of
methylamine in MeOH) in CH$_3$CN (7.0 mL) was stirred at rt for 10 min. After
adding excess pyridine (1.0 mL, 12 mmol), the mixture was stirred overnight
and then evaporated *in vacuo* to give a residue. The residue was dissolved
in MeOH and subjected to purification by preparative reverse phase HPLC.
Separation method: Start %B = 30, Final %B = 80, Gradient time = 8 min,
Flow Rate = 25 mL/min, Column: YMC C18 S5 20 x 100mm. ^{1}H NMR
(mixture of conformers, CD$_3$OD) δ 8.39 (app b s, 1H), 8.12 and 8.08 (s, 1H),
7.70 (app b s, 1H), 7.44 (b s, 5H), 7.34 (app b s, 1H), 5.00 – 3.00 (b m, 7H),
2.97 (s, 3H), 1.38 – 1.25 (b m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 433, HPLC
R$_t$ = 1.240.

143
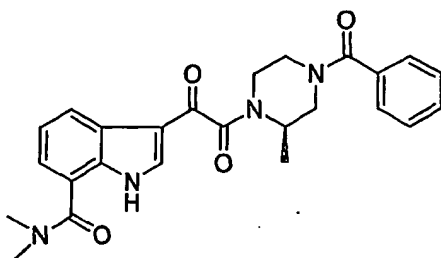
EXAMPLE 65

Prepared as described above in Example 64 using dimethylamine as the amine component. Separation method: Start %B = 40, Final %B = 100, Gradient time = 8 min, Flow Rate = 25 mL/min, Column: YMC C18 S5 20 x 100mm. ^{1}H NMR (mixture of conformers, CD$_3$OD) δ 8.31 (app b s, 1H), 8.12 and 8.07 (s, 1H), 7.60 – 7.10 (b overlapping m, 7H), 5.10 – 3.00 (b m, 7H), 3.30 (s, 3H), 3.00 (s, 3H), 1.36 – 1.24 (b m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 447, HPLC R$_t$ = 1.260.
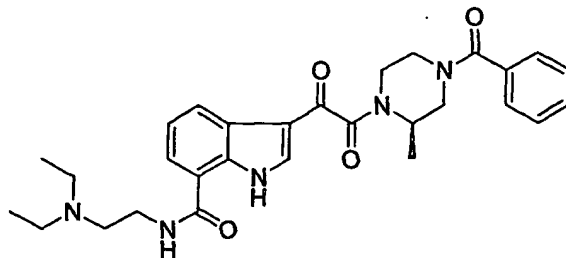
EXAMPLE 66

Prepared as described above in Example 64 using N,N-diethylethylenediamine as the amine component. Separation method: Start %B = 30, Final %B = 80, Gradient time = 8 min, Flow Rate = 25 ml/min, Column: YMC C18 S5 20 x 100mm. ^{1}H NMR (mixture of conformers, 300 MHz, CD$_3$OD) δ 8.47 – 8.45 (app b m, 1H), 8.15 and 8.12 (s, 1H), 7.82 – 7.79 (app b d, 1H), 7.47 – 7.37 (b overlapping m, 6H), 5.00 – 3.00 (b overlapping m, 7H), 3.84 (t, J = 9.9, 2H), 3.45 (t, J = 9.9, 2H), 3.33 (q, J = 12.1, 4H), 1.39 (t, J = 12.1, 6H), 1.10 – 1.45 (b m overlapped with t, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 518, HPLC R$_t$ = 1.147.

144
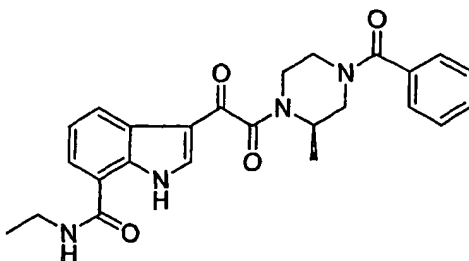
EXAMPLE 67

A mixture of the acid chloride (as shown in Example 64) (*ca.* 0.03 mmol) in neat ethylamine (0.5 ml, 7.6 mmol) was stirred at rt for 2 h. The
5   excess amine was then removed by evaporation *in vacuo* to give a residue, which was dissolved in MeOH and subjected to purification by preparative reverse phase HPLC. Separation method: Start %B = 30, Final %B = 100, Gradient time = 9 min, Flow Rate = 25 mL/min, Column: YMC C18 S5 20 x 100mm. ^{1}H NMR (mixture of conformers, $CDCl_3$) δ 11.10 (b s, 1H), 8.50 (app
10   b s, 1H), 8.052, 8.046 and 8.037 (s, 1H), 7.49 – 7.34 (b overlapping m, 6H), 6.49 (b s, 1H), 5.10 – 2.90 (b m, 7H), 3.59 – 3.53 (overlapping q, 2H), 1.50 – 1.10 (b m overlapped with t, 3H), 1.31 (t, J = 7.3, 3H); LC/MS (ES+) m/z $(M+H)^+$ = 447, HPLC R_t = 1.330.
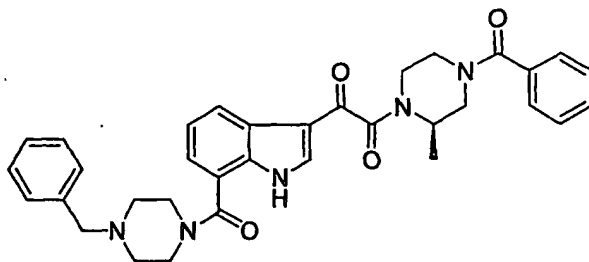
15   ## EXAMPLE 68

Prepared as described above in **Example 64** using monobenzyl piperazine as the amine component. The product precipitated from a MeOH
20   solution, and was filtered and washed with MeOH to provide a analytical pure sample; ^{1}H NMR (mixture of conformers, $CDCl_3$) δ 11.7 (b s, 1H), 8.38, (app b s, 1H), 7.76–7.16 (overlapping m, 13H), 4.93–2.88 (overlapping m, 15H), 2.47 (s, 2H), 1.25 (b s, 3H); LC/MS (ES+) m/z $(M+H)^+$ = 578, HPLC R_t = 1.210.

EXAMPLE 69
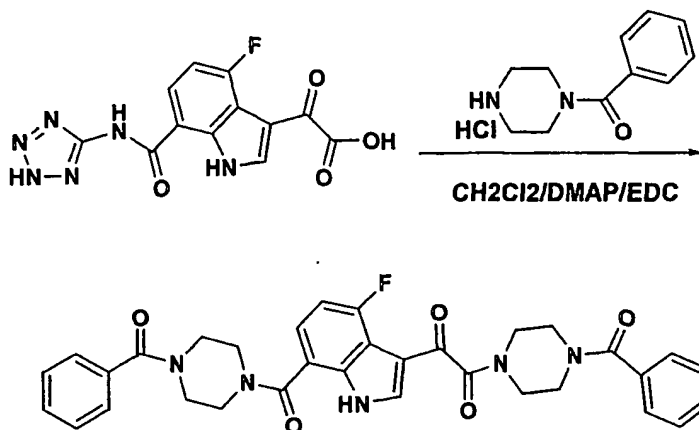
The product shown above was isolated as an unexpected product from the above reaction. Separation method: Start %B = 30, Final %B = 100, Gradient time = 12 min, Flow Rate = 30 mL/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 4.89 – 5.42 min. ^{1}H NMR (300 MHz, CD$_3$OD) δ 8.21 (s, 1H), 7.48 (b s, 10H), 7.39 (app, dd, J = 7.8, 4.3, 1H), 7.06 (app, t, J = 9.3, 1H), 4.10 – 3.36 (b m, 16H); LC/MS (ES+) m/z (M+H)$^+$ = 596, HPLC R$_t$ = 1.330.
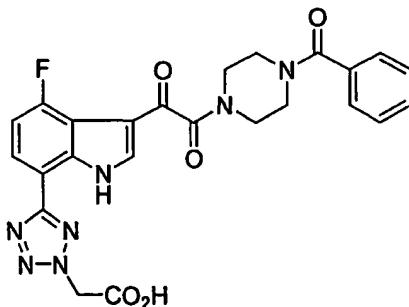
EXAMPLE 70

To a mixture of the methyl ester (Compound of Example 22), (100.0 mg, 0.193 mmol) in MeOH (1.5 mL) was added NaOH (0.4 mL, 0.4 mmol, 1 N, aq.). The resulting mixture was stirred at rt for 4 h and then concentrated under a stream of nitrogen. The residue was diluted with excess H$_2$O (~ 6 mL) and acidified to pH ~1 with HCl (1 N, aq.) to induce precipitation. The precipitates were filtered, washed with H$_2$O (3 x 1 mL) and dried under high vacuum to give the product as an off white solid (85.7 mg, 88%). ^{1}H NMR

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(CD₃OD) δ 8.24 (s, 1H), 8.16 (b dd, 1H), 7.46 (b s, 5H), 7.16 (app t, 1H), 5.69 (s, 2H), 4.00 – 3.45 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 506, HPLC R$_t$ = 1.320.

5   **EXAMPLE 71**
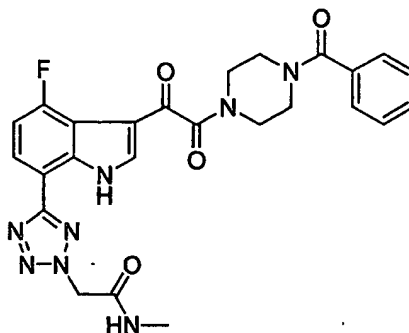
To a mixture of the acid (Compound of Example 70), (19.8 mg, 39.2 μmol) in DMF (1.0 mL) was added methylamine hydrochloride (17.0 mg, 0.252 mmol), HOBT (19.2 mg, 0.142 mmol), EDC (27.2 mg, 0.142 mmol) and NMM (35 μL, 0.318 mmol), and the resulting mixture stirred at rt for 24 h. The volatile was then evaporated under high vacuum to give a residue, which was diluted with H₂O (~ 5 mL) and acidified to pH ~1 with HCl (1 *N*, aq.). The precipitates were filtered, washed with H₂O (1 mL) and then HCl (1 mL, 1 *N*, aq.). The crude product was purified by preparative TLC (5% MeOH/CH₂Cl₂, 500 μm x 20 cm x 20 cm plate) to give the product as a white solid. ¹H NMR (CDCl₃) δ 11.34 (s, 1H), 8.18 (d, *J* = 2.4, 1H), 8.09 (dd, *J* = 8.3, 4.3, 1H), 7.41 (b s, 5H), 7.09 (app t, 1H), 5.40 (s, 2H), 4.00 – 3.40 (b m, 8H) 2.85 (s, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 519, HPLC R$_t$ = 1.203.
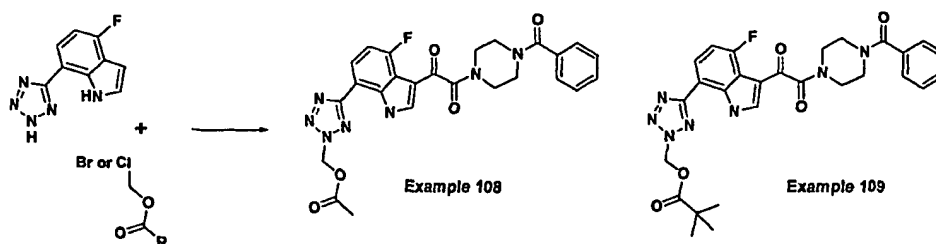
EXAMPLE 72
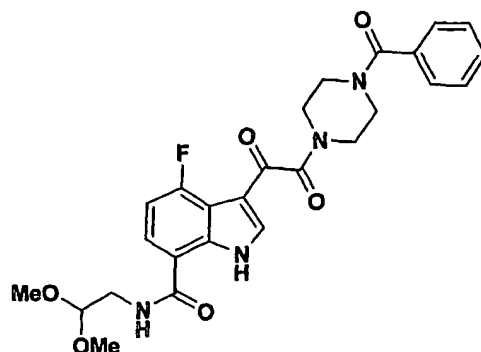
To a suspension of the acid, Intermediate 23, (250 mg, 0.590 mmol) in CH_2Cl_2 (5 mL), was added DMAP (116 mg, 0.949 mmol), aminoacetaldehyde
5   dimethyl acetal (80 μl, 0.734 mmol) and EDC (136 mg, 1.142 mmol), and the resulting mixture stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (40 mL), washed with HCl (3 x 20 mL, 1 N aq.), and then water (40 mL). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give the product as pale yellow solid (226 mg, purity: 90% HPLC), which was
10   used for the next step without further purification. ^{1}H NMR (CD_3OD) δ 8.17 (s, 1H), 7.77 (app t, J = 9.2, 1H), 7.46 (b s, 5H), 7.02 (app dd, J = 20.4, 11.6, 1H), 4.60 (t, J = 5.3, 1H) 3.97 – 3.44 (b m, 10H, overlapped with singlets), 3.55 (s, 3H), 3.54 (s, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 511, HPLC R_t = 1.210.

15   **EXAMPLE 73**
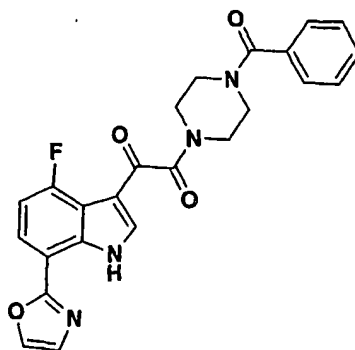
To the compound of Example 72 (75 mg, 0.147 mmol) was added the Eaton reagent (0.5 mL, freshly prepared by heating a suspension of

phosphorous pentoxide (100 mg, 0.705 mmol) in methanesulfonic acid (1 mL, 0.015 mmol) at 90 °C for 3 h). The resulting mixture was stirred at 130 °C for 10.5 h. After cooling down to rt, the reaction mixture was added ice water (ca. 10 mL) while vigorously stirred. The solid residue was filtered, and
5   dissolved in a mixture of DMF/MeOH for purification by reverse phase preparative HPLC using the method: Start %B = 20, Final %B = 90, Gradient time = 15 min, Flow Rate = 25 mL/min, Column: YMC C18 S5 20 x 100mm, Fraction Collection: 11.03 – 11.59 min. ^{1}H NMR (CD$_3$OD) δ 8.24 (s, 1H), 8.03 (app s, 1H), 7.95 (app dd, J = 7.6, 4.1, 1H), 7.46 (b s, 5H), 7.42 (app s, 1H),
10   7.13 (app t, J = 8.8, 1H), 3.96 – 3.44 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 447, HPLC R$_t$ = 1.367.

EXAMPLE 74
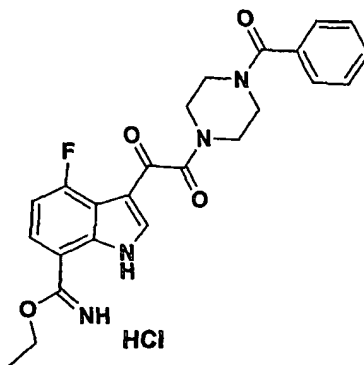
15   Intermediate 12, (100 mg, 0.247 mmol) was placed in a reusable sealed tube was dissolved in a solution of HCl in dioxane (3 mL, 4 M). To the solution was added EtOH (0.6 mL, 10.4 mmol, 200 proof, anhydrous, 99.5+% from Aldrich). The reaction mixture was cooled to –5 °C and bubbled with dry hydrochloride gas, while stirred, for 1 h. The reaction flask was then sealed
20   and the reaction mixture stirred at rt for 17 h. Evaporation of the volatile in vacuo gave the product as a yellow oil, which was used without further purification. LC/MS (ES+) m/z (M+H)$^+$ = 451, HPLC R$_t$ = 1.093, purity: 91%.

149
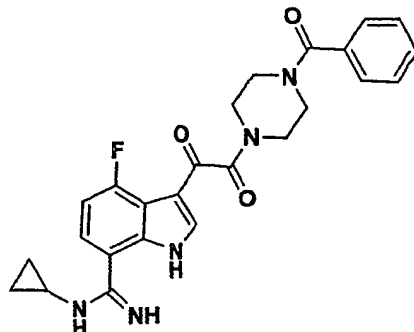
EXAMPLE 75

To a solution of the compound of Example 74 (*ca.* 0.06 mmol) in EtOH

5   (0.5 mL) was added cyclopropylamine (14 µl, 0.20 mmol). After stirring at rt for 16 h, the reaction mixture was diluted with MeOH (2 mL), and subjected to purification by preparative HPLC using the method: Start %B = 10, Final %B = 75, Gradient time = 15 min, Flow Rate = 25 mL/min, Column: YMC C18 S5 20 x 100mm, Fraction Collection: 7.44 – 8.17 min. ^{1}H NMR (CD$_3$OD)

10   δ 8.27 (s, 1H), 7.56 (app dd, J = 8.3, 4.2, 1H), 7.46 (b s, 5H), 7.15 (app t, J = 9.2, 1H), 3.96 – 3.35 (b m, 8H), 2.86 (m, 1H), 1.08 (m, 2H), 0.92 (m, 2H); LC/MS (ES+) m/z (M+H)$^+$ = 462, HPLC R$_t$ = 0.983.

EXAMPLE 76

15
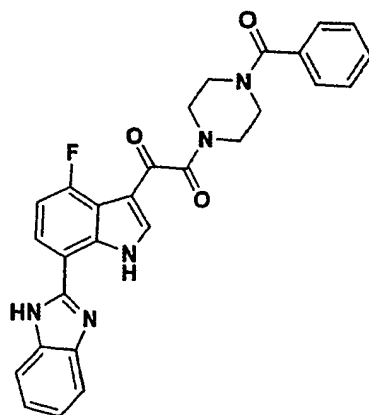
To a solution of the compound of Example 74 (*ca.* 0.083 mmol) in EtOH (0.5 mL) was added 1,2-phenylenediamine (26.0 mg, 0.24 mmol) and *N,N*-diisopropylethylamine (0.1 mL, 0.574 mmol). After stirring at 90 °C for

16 h, the reaction mixture was cooled to rt, diluted with MeOH (2 mL), and then subjected to purification by preparative HPLC using the method: Start %B = 20, Final %B = 75, Gradient time = 15 min, Flow Rate = 25 mL/min, Column: YMC C18 S5 20 x 100mm, Fraction Collection: 10.33 – 11.05 min.

5   ^{1}H NMR (CD$_3$OD) δ 8.33 (s, 1H), 7.90 (app, t, J = 3.8, 1H), 7.76 (app dd, J = 6.0, 3.1, 2H), 7.46 (b s, 7H), 7.23 (app d, J = 9.2, 1H), 3.90 – 3.44 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 496, HPLC R$_t$ = 1.277.

EXAMPLE 77

10
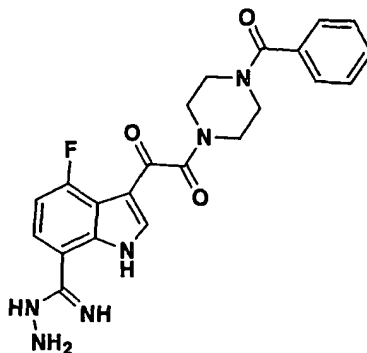
To a solution of the compound of Example 74 (ca. 0.166 mmol) in EtOH (0.5 ml) was added hydrazine (20 μl, 0.631 mmol, anhydrous) and N,N-diisopropylethylamine (0.1 mL, 0.574 mmol). The reaction mixture was

15   stirred at rt for 16 h. Removal of solvent in vacuo afforded the product as a brown oil which was used for the next step without further purification. LC/MS (ES+) m/z (M+H)$^+$ = 437, HPLC R$_t$ = 0.913, purity: 50%.
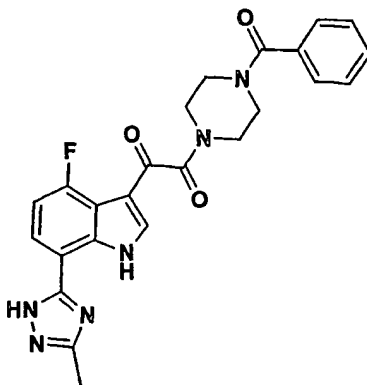
EXAMPLE 78

To a solution of the compound of Example 77 (*ca.* 0.083 mmol) in pyridine (0.5 mL) was added acetyl chloride (12 µl, 0.17 mmol). After stirring

5   at 110 °C for 16 h, the reaction mixture was cooled to rt , diluted with MeOH (2 mL), and then subjected to purification by preparative reverse phase HPLC using the method: Start %B = 20, Final %B = 80, Gradient time = 12 min, Flow Rate = 25 mL/min, Column: YMC C18 S5 20 x 100mm, Fraction Collection: 8.57 – 9.17 min. ^{1}H NMR (CD$_3$OD) δ 8.21 (s, 1H), 7.96 (app d, *J*

10   = 7.9, 1H), 7.46 (b s, 5H), 7.09 (app t, *J* = 9.0, 1H), 3.98 – 3.44 (b m, 8H), 2.57 (s, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 461, HPLC R$_t$ = 1.270.

EXAMPLE 79
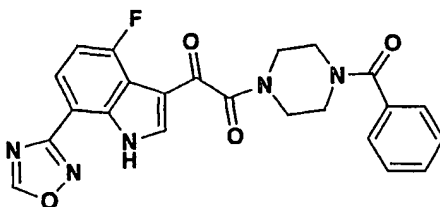
15   A suspension of the compound of Example 27 (32 mg, 0.073 mmol) in triethylorthoformate (0.5 mL, 3.0 mmol) was stirred at 105 °C for 16 h. After cooling down to rt, the reaction mixture was added to MeOH (2 mL), and then subjected to purification by preparative reverse phase HPLC using the method: Start %B = 10, Final %B = 80, Gradient time = 15 min, Flow Rate =

20   25 ml/min, Column: YMC C18 S5 20 x 100mm, Fraction Collection: 11.49 – 12.29 min. ^{1}H NMR (CD$_3$OD) δ 9.41 (s, 1H), 8.23 (s, 1H), 8.15 (app t, *J* =

6.3, 1H), 7.46 (b s, 5H), 7.17 (app t, *J* = 9.3, 1H), 3.91 – 3.44 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$= 448, HPLC R$_t$ = 1.387.

EXAMPLE 80
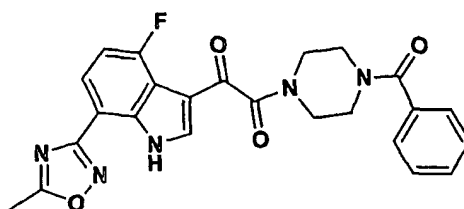
To a mixture of the compound of Example 27 (24 mg, 0.055 mmol) in pyridine (0.5 mL) was added acetyl chloride (9 µl, 0.121 mmol) and the resulting mixture stirred at 115 °C for 16 h. After cooling down to rt, the reaction mixture was added to MeOH (2 mL), and then subjected to purification by preparative reverse phase HPLC using the method: Start %B = 10, Final %B = 100, Gradient time = 15 min, Flow Rate = 25 mL/min, Column: YMC C18 S5 20 x 100mm, Fraction Collection: 10.28 – 11.08 min. ^{1}H NMR (CD$_3$OD) δ 8.22 (s, 1H), 8.06 (app d, *J* = 5.0, 1H), 7.46 (b s, 5H), 7.15 (app t, *J* = 8.6, 1H), 3.87 – 3.34 (b m, 8H), 2.72 (s, 3H); LC/MS (ES+) m/z (M+H)$^+$= 462, HPLC R$_t$ = 1.453.

EXAMPLE 81
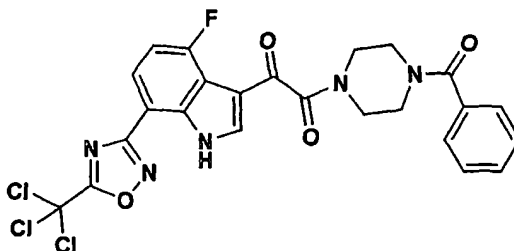
A suspension of the compound of Example 27 (100 mg, 0.229 mmol) in trichloroacetic anhydride (1 mL, 5.48 mmol) was stirred at 80 °C for 16 h. After cooling down to rt, the reaction mixture was poured into MeOH (20 mL) and left standing for 1 h. The precipitates were filtered, washed with MeOH (3 x 3 mL) and dried under high vacuum to give the product as a white solid

(74 mg, 57%). Alternatively, after cooling down to rt, the reaction mixture was poured carefully into water and extracted with EtOAc (x 3). The combined organic extracts were dried (MgSO$_4$) and evaporated *in vacuo* to give a yellow residue, which was purified by flash chromatography (Hexane then EtOAc/Hexane (50% to 60% to 70%)). ^{1}H NMR (CDCl$_3$) δ 10.41 (s, 1H), 8.25 (d, *J* = 3.1, 1H), 8.18 (app dd, *J* = 8.4, 4.4, 1H), 7.47 (b s, 5H), 7.16 (app t, *J* = 9.3, 1H), 3.87 – 3.34 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 565, HPLC R$_t$ = 1.843.
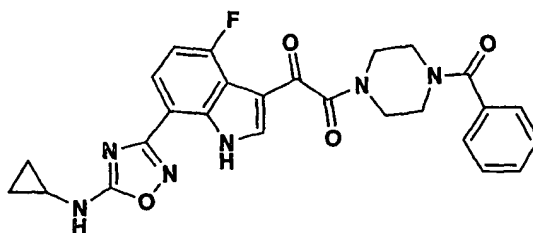
EXAMPLE 82

To a mixture of the compound of Example 81 (20 mg, 0.035 mmol) in DMF (0.5 mL) was added cyclopropylamine (0.1 mL, 1.426 mmol) and the resulting mixture stirred at rt for 16 h. Hydrochloric acid (1 *N*, *aq.*) was then added slowly to the reaction mixture until precipitates formed (pH about 6). The precipitates were filtered, washed three times with water, and dried under high vacuum to give the product as a white solid. (11 mg, 62%). ^{1}H NMR (CDCl$_3$) δ 10.71 (s, 1H), 8.16 (d, *J* = 3.0, 1H), 7.99 (app dd, *J* = 8.3, 4.4, 1H), 7.47 (b s, 5H), 7.08 (app t, *J* = 9.4, 1H), 5.73 (s, 1H), 3.83 – 3.49 (b m, 8H), 2.90 (b m, 1H), 0.94 (b m, 2H), 0.77 (b m, 2H); LC/MS (ES+) m/z (M+H)$^+$ = 503, HPLC R$_t$ = 1.513.

EXAMPLE 83

● ●
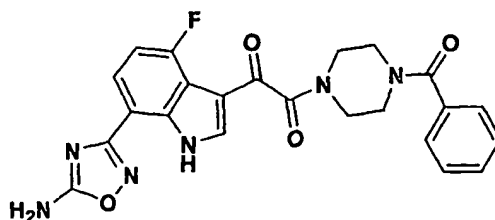
To a mixture of the compound of Example 81 (25 mg, 0.044 mmol) in DMF (0.3 mL) was added a saturated solution of ammonia in MeOH (0.2 mL) and the resulting mixture stirred at rt for 16 h. The reaction mixture was added to MeOH (2 mL), and then subjected to purification by preparative

5   reverse phase HPLC using the method: Start %B = 20, Final %B = 100, Gradient time = 12 min, Flow Rate = 40 mL/min, Column: YMC C18 S5 30 x 100mm, Fraction Collection: 7.68 – 8.08 min. ^{1}H NMR (CDCl$_3$) δ 10.61 (s, 1H), 8.17 (d, J = 3.0, 1H), 7.93 (app dd, J = 8.4, 4.4, 1H), 7.43 (b s, 5H), 7.09 (app t, J = 9.7, 1H), 5.52 (s, 2H), 3.97 – 3.52 (b m, 8H); LC/MS (ES+) m/z

10   (M+H)$^+$ = 463, HPLC R$_t$ = 1.303.

EXAMPLE 84
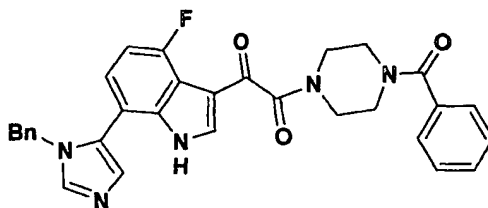
A mixture of the acid chloride **intermediate 26** and benzoylpiperazine

15   hydrochloride (24.9 mg, 0.110 mmol) in THF (2.0 ml) was added diisopropylethylamine (0.1 ml, 0.574 mmol) dropwise. After stirring for 5 hours, the reaction mixture, which contained mostly the acid of **intermediate 26**, was added EDC (21.1 mg, 0.110 mmol), DMAP (22.4 mg, 0.183 mmol) and DMF (1 ml), and then stirred for another 91 hours. The volatile was

20   evaporated under a stream of nitrogen and the residue added excess water (about 10 ml) to induce precipitation. The off white solid was filtered, and washed with water (3 x 3 ml) and dried under a stream of air. The crude solid was purified by preparative TLC (5% MeOH/CH$_2$Cl$_2$, 1 x 500 m x 20 cm x 20 cm plate). The silica gel of the product band was removed from the plate,

25   loaded onto a filter funnel, and washed with 10% MeOH/CH$_2$Cl$_2$ (3 x 5 ml). The combined washings were evaporated *in vacuo* to give the product as an off white solid (22.7 mg, 46% 2 steps). ^{1}H NMR: (CDCl$_3$) δ 13,24 (b s, 1H), 8.13 (d, J = 2.5, 1H), 7.43 (b s, 5H), 7.25-7.20 (overlapping m, 4H), 7.03-6.97 (overlapping m, 2H), 6.90 (s, 1H), 6.81 (d, J = 7.4, 2H), 4.84 (s, 2H), 3.83-

30   3.49 (b m, 8 H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 536, HPLC R$_t$ = 1.197.

● ●

155

EXAMPLE 85
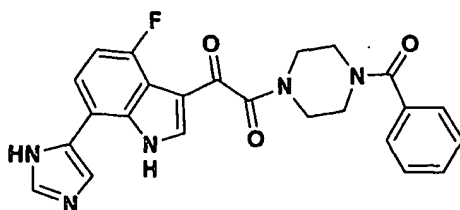
To a mixture of the compound prepared in **Example 84** (12.0 mg, 22.4

μmol) in MeOH (2.0 ml) was added 10% Pd/C (25 mg). After stirring at room

5 temperature for 24 hours, the 50% converted (based on LC/MS analysis)

reaction mixture was filtered through a Whatman PDVF disc filter (0.45 μm).

The residue obtained after evaporation of the filtrate was purified by

preparative TLC (10% MeOH/CH$_2$Cl$_2$, 2 x 500 m x 20 cm x 20 cm plates).

The silica gel of the product band was removed from the plate, loaded onto a

10 filter funnel, and washed with 10% MeOH/CH$_2$Cl$_2$ (3 x 5 ml). The combined

washings were evaporated *in vacuo* to give the product as a white solid. ^{1}H

NMR: (CD$_3$OD/CDCl$_3$) δ 8.02 (s, 1H), 7.76 (s, 1H), 7.45-7.30 (overlapping m,

7H), 6.85 (b s, 1H), 3.90-3.40 (b m, 8 H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 446,

HPLC R$_t$ = 0.960.

15

EXAMPLE 86
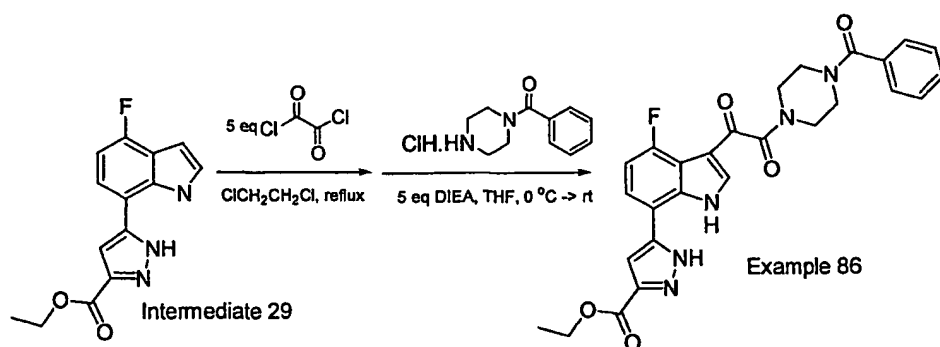
20 An oven dried 50 ml flask was charged with the ethyl pyrrazole-3-

carboxylate compound **intermediate 29** (149 mg, 0.513 mmol) and 1,2-

dichloroethane to give a solution, which at rt. was added neat oxalyl chloride

(228 μl, 2.56 mmol) dropwise *via* a syringe. The reaction mixture was

refluxed at about 85°C for 2 h., cooled to rt, and the volatile evaporated *in*

vacuo to give the crude indoleglyxoyl chloride. A mixture of the indoleglyxoyl chloride in dry THF (10 ml) at rt was added benzoylpiperazine hydrochloride (107 mg, 0.472 mmol), and then stirred for 10 min. *N,N*-diisopropylethylamine (447 µl, 2.56 mmol) was then added dropwise to the

5   mixture cooled to 0°C in an ice-water bath, and the resulting reaction mixture stirred for 10 min. The reaction mixture was warmed to rt and stirred for another 1 hr. After evaporation *in vacuo* to remove part of the solvent, the crude mixture was added MeOH (3 ml), and purified by preparative reverse phase HPLC to afford 102 mg of light solids. Recrystalization of the solids

10   from hot MeOH gave, after drying, the product as (50 mg, 19%) of white solid. ^{1}H NMR (CD$_3$OD) 8.21 (s, 1H), 7.68-7.74 (m, 1H), 7.41-7.54 (b s, 5H), 7.36 (s, 1H), 7.06 (m, 1H), 4.42 (q, J = 7.1, 2H), 3.45-4.0 (b m, 8H) 1.42 (t, J = 7.2, 3H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 518, HPLC (0.2% H$_3$PO$_4$ buffer, gradient time = 8 min, flow rate = 2.5 ml/min) R$_t$ = 6.20.

15

EXAMPLE 87

Intermediate 30   Example 87
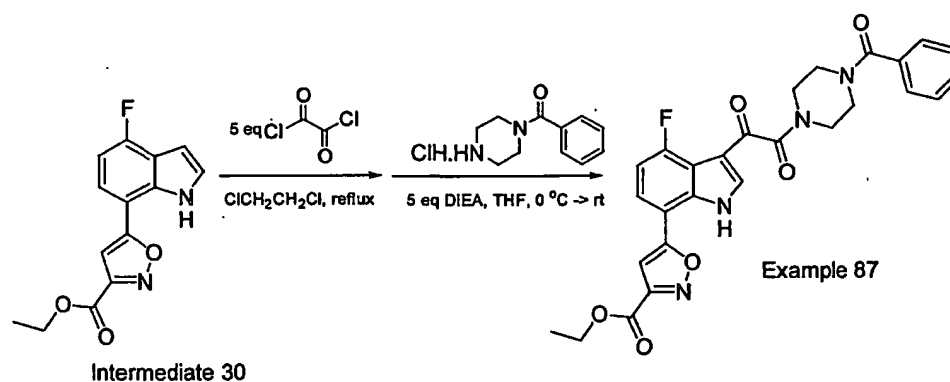
20   An oven dried 20 ml flask was charged with the ethyl isoxazole-3-carboxylate compound **intermediate 30** (56 mg, 0.204 mmol) and anhydrous 1,2-dichloroethane (3 ml). The mixture was stirred at rt for 5 min, added oxalyl chloride (89 µl, 1.02 mmol) and then refluxed at about 85°C for 3 h. After cooling to rt, the volatile was evaporated *in vacuo* to give the crude

25   indoleglyxoyl chloride. A mixture of the indoleglyxoyl chloride (40.8 mg, 0.112 mmol) in dry THF (4 ml) at rt was added benzoylpiperazine hydrochloride (23.4 mg, 0.103 mmol), and then stirred for 5 min. *N,N*-diisopropylethylamine (98 µl, 0.56 mmol) was then added dropwise to the mixture cooled to 0°C in an ice-water bath, and the resulting reaction mixture

stirred for 5 min. The reaction mixture was warmed to rt and stirred for another 1 hr. After evaporation *in vacuo* to remove part of the solvent, the crude mixture was added MeOH (3 ml), and purified by preparative reverse phase HPLC to give 28 mg of light yellow solids. Recrystallization of the

5 solids from hot MeOH gave the product (17 mg, 16%) as a white solid. ^{1}H NMR: (DMF-d_7, δ = 8.22 ppm) 13.08 (s, 1H), 8.65 (d, J = 3.5 1H), 8.3 (burried s, 1H), 7.82 (s, 1H), 7.68 (b s, 5H), 7.48 (t, J = 9.5, 1H), 4.67 (q, J = 7.2, 2H), 3.31-4.17 (b s, 8H), 1.59 (t, J = 7.5, 3H); LC/MS: (ES+) m/z (M+H)$^+$ = 519, HPLC (0.2% H_3PO_4 buffer, gradient time = 4 min, flow rate = 2 ml/min)

10 R_t = 4.147.

EXAMPLE 88

Example 86   10 eq NaOH, rt / EtOH, 7 hr   Example 88
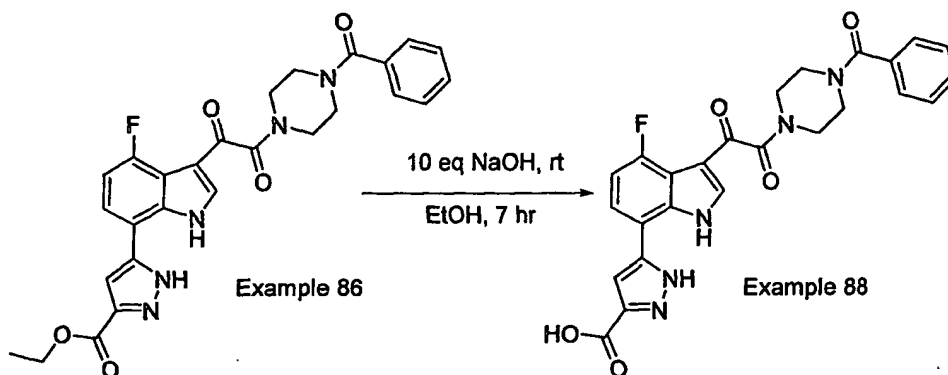
15

To a mixture of the compound prepared in **Example 86**, (75 mg, 0.145 mmol) in EtOH (5 ml) at rt was added NaOH (0.145 ml, 1.45 mmol, 10 N, aq), and the reaction mixture stirred at rt for 7 h. The reaction mixture was then neutralized with 10 N hydrochloric acid, and the crude product purified by

20 preparative reverse phase HPLC to afford the product (35.3 mg, 50%) as a light yellow solid. ^{1}H NMR (CD$_3$OD) δ 8.14 (s, 1H), 7.59-7.7.66 (m, 1H), 7.32-7.48 (b s, 5H), 7.26 (s, 1H), 7.00 (app t, J = 9.5, 1H), 3.35-3.95 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 490, HPLC (0.2% H_3PO_4 buffer, gradient time = 4 min, flow rate = 2 ml/min) R_t = 3.987.

25 This hydrolysis was also performed in MeOH using 5 equiv. of NaOH (1 N, aq).

EXAMPLE 89

Example 86   Example 89
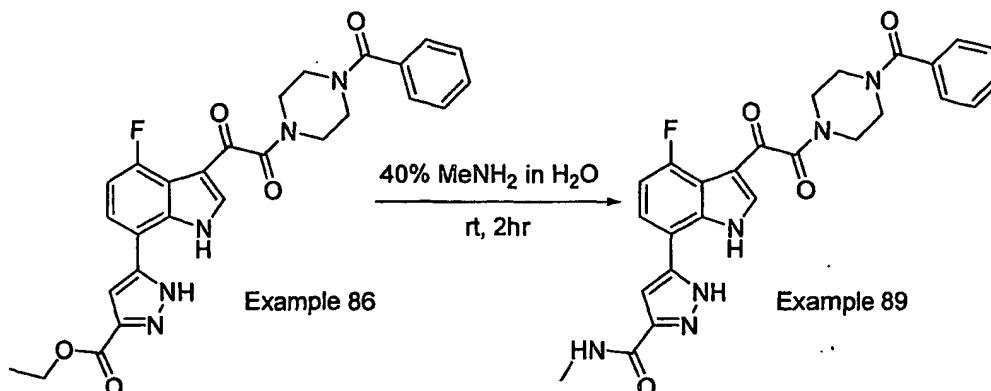
To a 2 ml vial was added the compound prepared in **Example 86** (10
mg, 0.0193 mmol) and excess $MeNH_2$ (2 ml, 40% in H_2O), and the reaction
mixture stirred at rt for 2 h. The crude product was then purified by reverse
phase preparative HPLC to afford the product (5.2 mg, 54%). ^1H NMR
(CD_3OD) 8.14 (s, 1H), 7.54 (dd, J = 4.2, 8.1, 1H), 7.31-7.48 (b s, 5H), 7.12
(s, 1H), 6.90 (overlapped dd, J = 8.5, 10.2, 1H), 3.20-3.95 (b m, 8H), 2.88 (s,
3H); **LC/MS:** (ES+) m/z $(M+H)^+$ = 503, HPLC (0.2% H_3PO_4 buffer, gradient
time = 4 min, flow rate = 2 ml/min) R_t = 3.837.

EXAMPLE 90
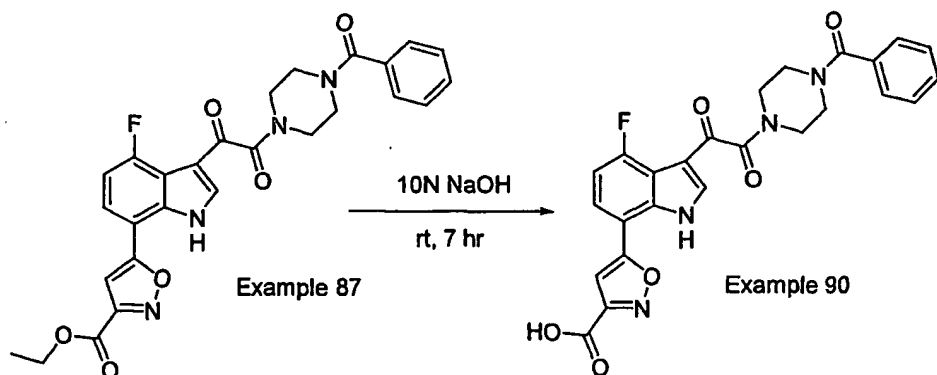
Example 87   Example 90

To a mixture of the compound prepared in **Example 87** (45 mg, 0.087
mmol) in EtOH (3 ml) at rt was added NaOH (0.09 ml, 0.87 mmol, 10 N, aq.),
and the reaction mixture stirred for 7 h. The reaction mixture was then
neutralized with 10 N hydrochloric acid, and the crude product purified by
reverse phase preparative HPLC to afford the product (28.5 mg, 67%) as a

light gray solid. ^{1}**H NMR** (CD$_3$OD) 8.23 (s, 1H), 7.84 (dd, J = 4.1, 8.5, 1H), 7.38-7.57 (b s, 5H), 7.29 (s, 1H), 7.15 (app t, J = 9.3, 1H), 3.45 – 3.98 (b m, 8H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 491, HPLC (0.2% H$_3$PO$_4$ buffer, gradient time = 4 min, flow rate = 2 ml/min) R$_t$ = 4.013.

5

Intermediate 23

Example 91

Example 92

Example 92

Example 93

Example 94
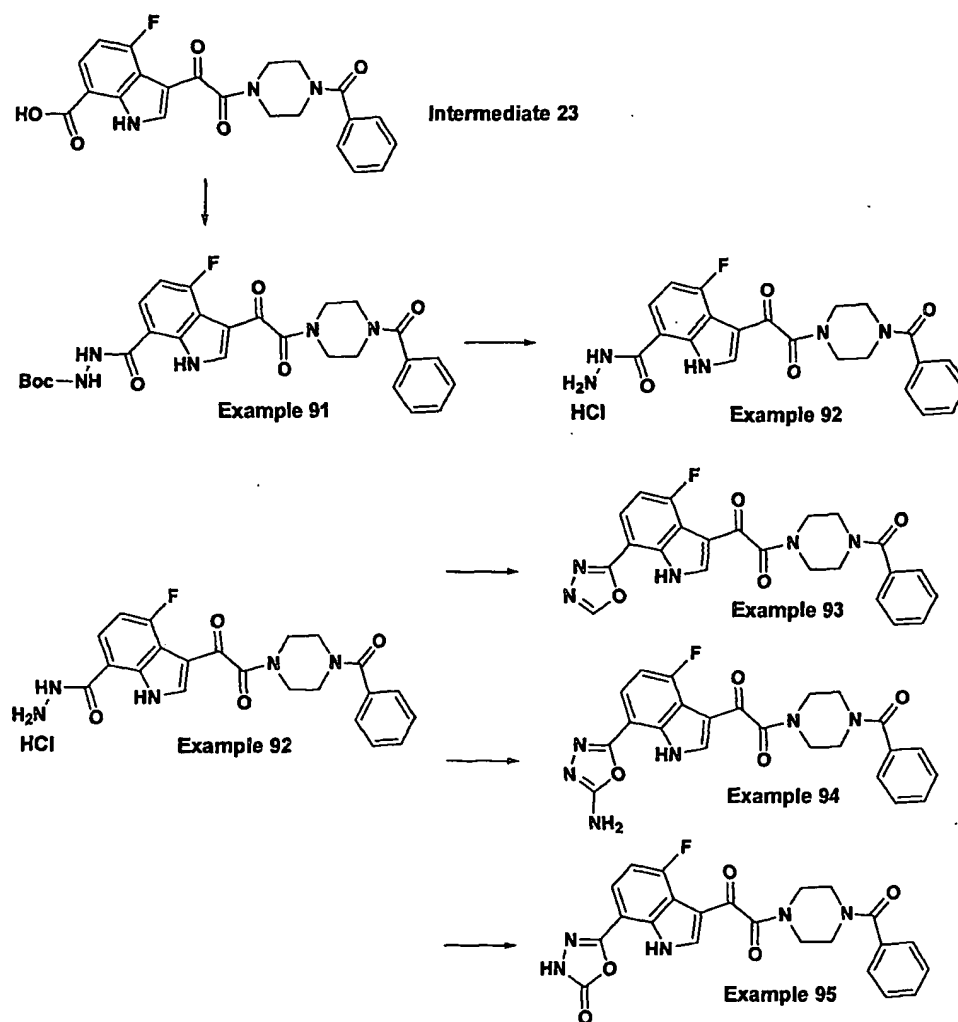
Example 95

EXAMPLE 91

10   To carboxylic acid **Intermediate 23** (300 mg, 0.71 mmol) in CH$_2$Cl$_2$ (10 ml) was added *tert*-butylcarbazate (140 mg, 1.06 mmol), DMAP (130 mg, 1.06 mmol), and EDC (203 mg, 1.06 mmol). The reaction mixture was stirred at room temperature for 16 hours. After dilution with CH$_2$Cl$_2$ (40 ml), the organic mixture was washed with hydrochloric acid (60 ml, 1 *N*) and water

15   (40 ml). Evaporation *in vacuo* gave a yellow solid which was purified by flash

chromatography using a gradient elution (hexane to 50% EtOAc/Hexane to EtOAc) to give the desired product as a pale yellow solid (300 mg, 79%). ^{1}H NMR: (CD$_3$OD) δ 8.18 (s, 1H), 7.80 (b m, 1H), 7.46 (b s, 5H), 7.04 (app t, J = 8.9, 1H), 3.85 – 3.51 (b m, 8H), 1.51 (s, 9H); LC/MS: (ES+) m/z (M+H)$^+$ = 538, HPLC R$_t$ = 1.343 min.

EXAMPLE 92

To the compound prepared in **Example 91** (300 mg, 0.558 mmol) was charged a solution of HCl in dioxane (3 ml, 12.0 mmol, 4 M), and the mixture stirred at room temperature for 4 hours. Removal of the excess reagent *in vacuo* afforded the hydrochloride salt of **Example 92** as a yellow solid (100% conversion). ^{1}H NMR: (CD$_3$OD) δ 8.21 (s,1H), 7.81 (app, dd, J = 8.4, 4.0, 1H), 7.46 (b s, 5H), 7.12 (app, t, J = 9.2, 1H), 3.95 – 3.49 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 438, HPLC R$_t$ = 1.023 min.

EXAMPLE 93

To the compound prepared in **Example 92** (18 mg) was added triethylorthoformate (0.5 ml, 3.01 mmol) and the resulting suspension stirred at 105°C for 16 hours. After cooling to room temperature, the reaction mixture was added MeOH (5 ml) and purified by reverse phase preparative HPLC using the method: Start %B = 30, Final %B = 90, Gradient time = 20 min, Flow Rate = 30 ml/min, Column : YMC C18 S5 30 x 100mm, Fraction Collection: 11.00 – 11.60 min. ^{1}H NMR: (DMSO) δ 12.56 (s, 1H), 9.48 (s,1H), 8.18 (app d, J =3.0, 1H), 7.97 (app dd, J = 8.3, 4.3, 1H), 7.44 (b s, 5H), 7.29 (app t, J = 9.3, 1H), 3.69 – 3.20 (b, m, overlapped with the solvent peak, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 448, HPLC R$_t$ = 1.317 min.

EXAMPLE 94

To the compound prepared in **Example 92** (15 mg) in dioxane (0.5 ml) was added a solution of cyanogen bromide in acetonitrile (0.1 ml, 0.5 mmol, 5.0 M) and a saturated aqueous solution of NaHCO$_3$ (0.1 ml). The resulting reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was then added MeOH (2 ml) and purified by reverse phase

preparative HPLC using the method: Start %B = 20, Final %B = 90, Gradient time = 18 min, Flow Rate = 30 ml/min, Column: YMC C18 S5 30 x 100mm, Fraction Collection: 11.42 – 12.03 min. **^{1}H NMR:** (CDCl$_3$) δ 10.65 (s, 1H), 8.22 (s,1H), 7.67 (app dd, J = 8.0, 4.1, 1H), 7.47 (b s, 5H), 7.10 (app t, J = 9.3, 1H), 6.83 (b s, 2H), 3.98 – 3.47 (b m, 8H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 463, HPLC R$_t$ = 1.273 min.

EXAMPLE 95

A solution of the compound of Example **92** (100 mg, 0.211 mmol) in EtOAc (50 ml) was washed with saturated aqueous NaHCO$_3$ solution (2 x 25 ml) and water (1 x 50 ml). After drying over MgSO$_4$, filtration, evaporation *in vacuo* and further dried under high vacuum, the resulting yellow solid was charged a solution of phosgene in toluene (5 ml, 1.92 *M*). The mixture was stirred at 110°C for 16 hours, then cooled to room temperature and added MeOH (5 ml) carefully. After removal of solvent *in vacuo*, the residue was dissolved in MeOH (10 ml) and purified by reverse phase preparative HPLC using the method: Start %B = 35, Final %B = 90, Gradient time = 15 min, Flow Rate = 25 ml/min, Column: YMC C18 S5 30 x 100mm, Fraction Collection: 6.66 – 7.23 min. **^{1}H NMR:** (DMSO-d_6) δ 12.85 (s, 1H), 12.17 (s, 1H), 8.14 (app d, J = 3.4, 1H), 7.73 (app dd, J = 8.3, 4.1, 1H), 7.44 (b s, 5H), 7.22 (app t, J = 9.4, 1H), 3.80 – 3.30 (b m, overlapped with solvent peak, 8H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 464, HPLC R$_t$ = 1.380 min.

EXAMPLE 96

Example 83   Example 96
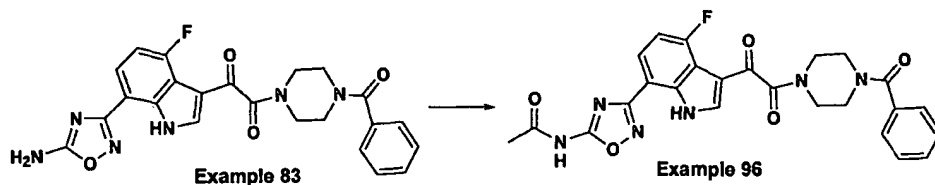
To a suspension of the compound prepared in **Example 83** (50 mg, 0.108 mmol) in toluene (1.0 ml) was added acetic anhydride (0.5 ml, 5.30 mmol). The resulting suspension was stirred at 110°C for 20 hours. After cooling to room temperature, the reaction mixture was filtered, and the solid residue obtained washed with MeOH (30 ml) to afford the product as a white

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solid (27 mg, 50%). **¹H NMR:** (DMSO-d_6) δ 12.36 (s, 1H), 12.16 (s, 1H), 8.16 (app d, J = 3.0, 1H), 7.95 (app dd, J = 8.3, 4.7, 1H), 7.44 (b s, 5H), 7.26 (app t, J = 9.3, 1H), 3.69 – 3.20 (b m, 8H), 2.24 (s, 3H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 505, HPLC R_t = 1.347 min.

EXAMPLE 97

Example 27   Example 97
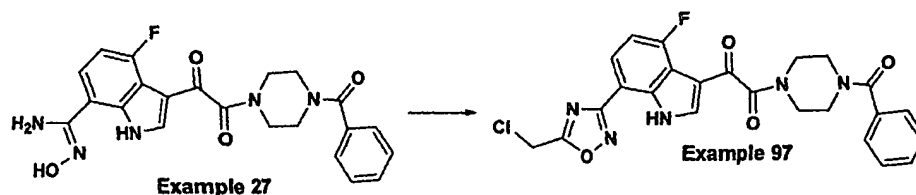
To the compound prepared in **Example 27** (15 mg, 80% pure, 0.027 mmol) was added chloroacetyl chloride (0.5 ml, 6.28 mmol). The resulting mixture was stirred at 50 °C for 16 hours. After cooling to room temperature, the reaction mixture was added MeOH (4 ml) and purified by reverse phase preparative HPLC using the method: Start %B = 25, Final %B = 100, Gradient time = 15 min, Flow Rate = 35 ml/min, Column: YMC C18 S5 30 x 100mm, Fraction Collection: 11.82 – 12.34 min. **¹H NMR:** (CDCl₃) δ 10.56 (s, 1H), 8.22 (app d, J = 3.0,1H), 8.11 (app dd, J = 8.3, 4.4, 1H), 7.47 (b s, 5H), 7.13 (app t, J = 9.3, 1H), 4.8(s, 2H), 3.98 – 3.50 (b, m, 8H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 496, HPLC R_t = 1.507 min.

Example 27   Example 98

Example 99   Example 100
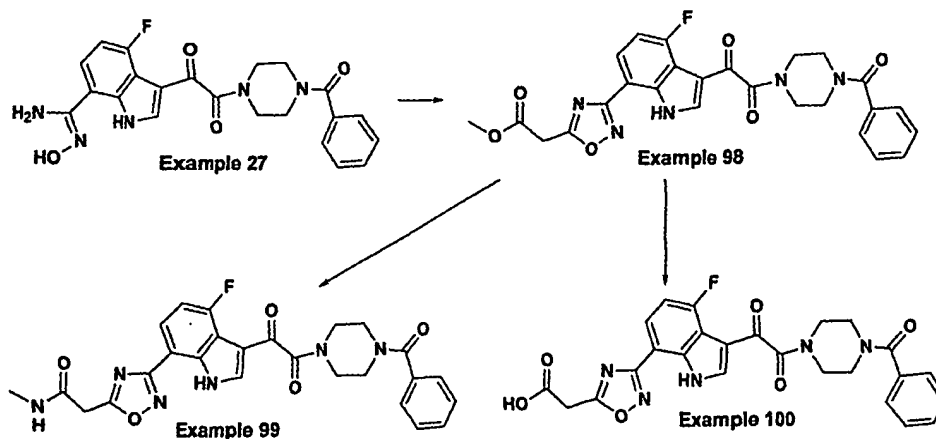
Example 98

To a solution of the compound prepared in **Example 27** (100 mg, about 80% pure, 0.18 mmol) in pyridine (1 ml), was added methyl malonyl chloride (0.5 ml, 4.66 mmol). The resulting reaction mixture was stirred at 50°C for 16 hours, then at 80°C for another 16 hours to complete the reaction. After cooling to room temperature, the reaction mixture was added MeOH (4 ml) and purified by reverse phase preparative HPLC using the method: Start %B = 20, Final %B = 90, Gradient time = 18 min, Flow Rate = 35 ml/min, Column: YMC C18 S5 30 x 100mm, Fraction Collection: 13.67 – 14.18 min. ^{1}H NMR: (CDCl$_3$) δ 10.61 (s, 1H), 8.21 (app d, J = 3.0,1H), 8.10 (app dd, J = 8.3, 4.4, 1H), 7.43 (b s, 5H), 7.12 (app t, J = 9.4, 1H), 4.14 (s, 2H), 3.83 (s, 3H, overlapped with b m), 3.98 – 3.52 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 520, HPLC R$_t$ = 1.407 min.

EXAMPLE 99

To the compound prepared in **Example 98** (10 mg, 0.019 mmol) was charged a solution of methylamine in water (0.5 ml, 40%). The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with MeOH (2 ml) and purified by reverse phase preparative HPLC using the method: Start %B = 25, Final %B = 90, Gradient time = 20 min, Flow Rate = 35 ml/min, Column: YMC C18 S5 3 x 100mm, Fraction Collection: 11.74 – 12.24 min. ^{1}H NMR: (CDCl$_3$) δ 10.5 (s, 1H), 8.21 (s,1H), 8.08 (app dd, J = 8.2, 4.4, 1H), 7.43 (b s, 5H), 7.13 (a t, J = 9.3, 1H), 6.69 (b s, 1H), 4.03 (s, 2H), 3.94 – 3.61 (b m, 8H), 2.94 (J = 4.8, 3H); LC/MS: (ES+) m/z (M+H)$^+$ = 519, HPLC R$_t$ = 1.283 min.

EXAMPLE 100

To a solution of the compound prepared in mple 98 (20 mg, 0.038 mmol) in MeOH (0.5 ml) was added an aqueous on of NaOH (0.5 ml, 1 N). The resulting mixture was stirred at room terature for 3 hours. After acidifying to pH about 2 using hydrochloric aci), the reaction mixture was added MeOH (2 ml) and purified by reverase preparative HPLC using the method: Start %B = 20, Final %B = radient time = 15 min, Flow Rate = 35 ml/min, Column: YMC C1 30 x 100mm, Fraction

Collection: 12.45 – 12.95 min. ¹H NMR: (CD₃OD) δ 8.23 (s, 1H), 8.11 (app dd, J = 7.7, 4.3, 1H), 7.47 (b s, 5H), 7.16 (app t, J = 8.6, 1H), 4.1.292 (s, 2H), 3.87 – 3.44 (b m, 8H); LC/MS: (ES+) m/z (M+H)⁺ = 506, HPLC R$_t$ = 1.340 min.
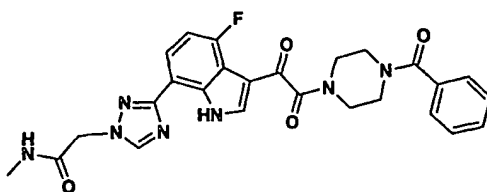
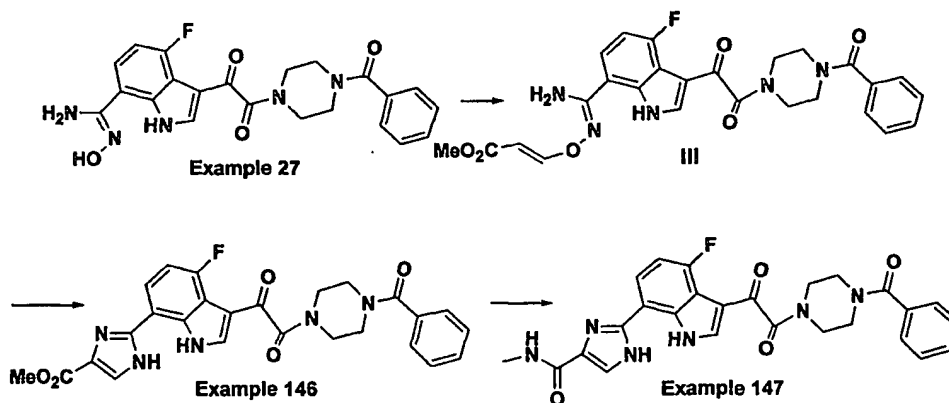

Example 27

Example 101
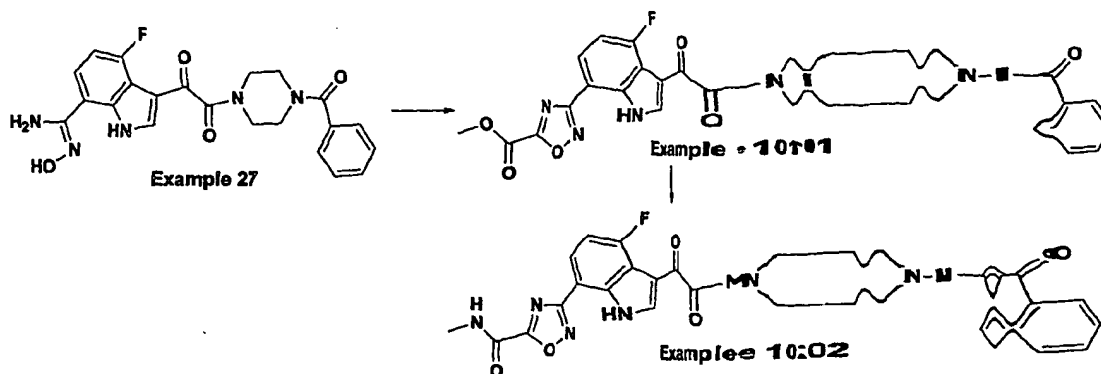
Example 102

EXAMPLE 101

To a solution of the compound prepared in Example 27 (500 mg, about 80% pure, 0.91 mmol) in pyridine (8 ml), was added methyl chlorooxoacetate (2.0 ml, 21.7 mmol). The resulting mixture was stirred at room temperature for 16 hours. Addition of MeOH (5 ml) and evaporation in vacuo afforded a brownish oil, which was purified by flash chromatography using a gradient elution (hexane to 20% to 50% to 80% EtOAc/Hexane to EtOAc) to give the desired product as a white solid (188 mg, 41 %). ¹H NMR: (CDCl₃) δ 10.54 (s, 1H), 8.23 (app d, J = 3.0, 1H), 8.20 (app d, J = 88.4, 4.4, 1H), 7.43 (b s, 5H), 7.15 (app t, J = 9.3, 1H), 4.16 (s, 3H), 3.88 — 3.3.-..49+9 (b m, 8H); LC/MS: (ES+) m/z (M+H)⁺ = 506, HPLC R$_t$ = 1.507 min.

EXAMPLE 102

To the compound prepared in Example 101 (15 mg, 0.030 mmol) was charged a solution of methylamine in water (1.0 ml, 40%). The resulting mixture was stirred at room temperature for 16 hours. After concentration in vacuo, the residue was purified by flash chromatography using a gradient elution (hexane to 10% to 50% to 80% EtOAc/Hexane to EtOAc) to give a yellow solid. The solid was washed with MeOH (3 ml) to give the desired product as a white solid (4.1 mg, 27%). ¹H NMR: (CDCl₃) δ 10.851 0 (s,s, 1H),

8.22 (app d, J = 3.0, 1H), 8.09 (app dd, J = 8.3, 4.4, 1H), 7.43 (b s, 5H), 7.23(m, 1H, overlapped with the solvent peak), 7.14 (app t, J = 9.2, 1H), 3.88 – 3.49 (b m, 8H), 3.13 (d, J = 5.1, 3H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 505, HPLC R_t = 1.423 min.

EXAMPLE 103

Example 101   Example 103

A mixture of the compound prepared in **Example 101** (25.0 mg, 49.5 mol) in THF (2.0 ml) in a reusable sealed tube was cooled to 0°C, and bubbled with ammonium gas for about 5 min. The sealed tube was closed tightly, and the reaction mixture stirred at room temperature for 3.5 hours. After which time, the volatile was evaporated under a stream of nitrogen, and water added to the residue. The white solid formed was filtered, washed with water (1 ml) and MeOH (2 x 0.5 ml), and dried to give a white solid (20.4 mg, 84%). ^{1}**H NMR:** (DMSO-d$_6$) δ 12.4 (s, 1H), 8.96 (s, 1H), 8.56 (s, 1H), 8.24 (d, J = 3.0, 1H), 8.09 (dd, J = 4.5, 8.5, 1H), 7.44 (b s, 5H), 7.30 (app t, 1H), 3.85 – 3.30 (b m, 8H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 491, HPLC R_t = 1.363.

EXAMPLE 104

Example 70   Example 104
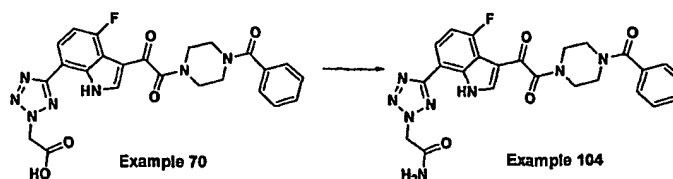
To a mixture of the acid which is the product of Example 70 (130.1 mg, 0.257 mmol) in DMF (2.5 ml) was added ammonium chloride (57.2 mg, 1.07 mmol), HOBT (169.7 mg, 1.26 mmol), EDC (241.0 mg, 1.26 mmol) and NMM (0.3 ml, 2.73 mmol), and the resulting mixture stirred at room temperature for 24 hours. The volatile was then evaporated under high vacuum to give a residue, which was diluted with H$_2$O (~ 5 ml) and acidified to pH ~1 with HCl (1 N, aq.). The aqueous solution was decanted, and the

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residue washed with HCl (3 x 2 ml, 1 *N*, aq.) and dried under high vacuum. The dried residue was then added a minimun amount of MeOH (1.5 ml) to induce precipitation. The precipitates were filtered, and washed successively with MeOH (0.5 ml), H_2O (2 x 1 ml), HCl (2 x 1 ml, 1 *N*, aq.) and MeOH (3 x

5   0.5 ml) to give the product as a light beige solid (54.2 mg, 42%). ^1H **NMR:** (CD_3OD) δ 8.25 (s, 1H), 8.15 (dd, *J* = 4.4, 8.0, 1H), 7.47 (b s, 5H), 7.16 (app t, 1H), 5.59 (s, 2H), 3.89 – 3.54 (b m, 8H); **LC/MS:** (ES+) m/z $(M+H)^+$ = 505, HPLC R_t = 1.113.

R = OMe Example 105A
R = OH Example 106A

Example 107A

10
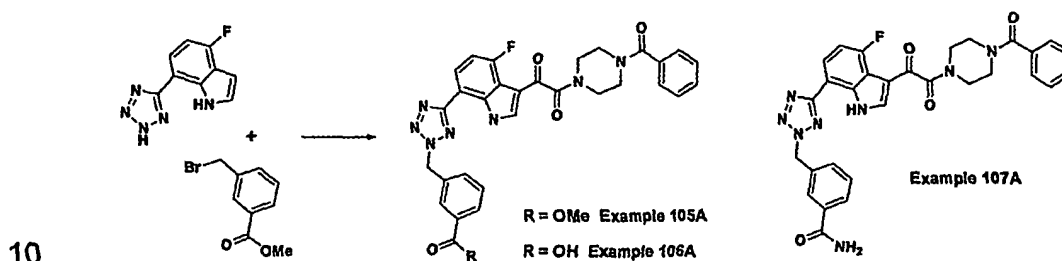
The products of **Examples 105A, 106A, and 107A,** and their ortho and para isomers were prepared analogously to those of **Examples 22, 70,** and **104** respectively. The corresponding benzyl bromide was prepared from

15   bromination of methyl toluate using NBS/benzoyl peroxide in CCl_4.

EXAMPLE 105A

^1H **NMR:** ($CDCl_3$) δ 10.95 (b s, 1H), 8.21 (d, *J* = 2.9, 1H), 8.17 (s, 1H), 8.11 –

20   8.07 (overlapping m, 2H), 7.64 (d, *J* = 7.8, 1H), 7.51 (t, *J* = 7.7, 1H), 7.43 (b s, 5H), 7.11 (app t, 1H), 5.92 (s, 2H), 4.00 – 3.45 (b m, 8H), 3.94 (s, 3H); **LC/MS:** (ES+) m/z $(M+H)^+$ = 596, HPLC R_t = 1.703.

EXAMPLE 106A

25

^1H **NMR:** (CD_3OD) δ 8.24 (s, 1H), 8.14 (s, 1H), 8.12 (m. 1H), 8.03 (d, *J* = 7.7, 1H), 7.71 (d, *J* = 7.9, 1H), 7.53 (t, *J* = 7.7, 1H),7.46 (b s, 5H), 7.14 (app t, 1H), 6.07 (s, 2H), 4.00 – 3.45 (b m, 8H); **LC/MS:** (ES+) m/z $(M+H)^+$ = 582, HPLC R_t = 1.627.

Example 107a

¹H NMR: (CD₃OD) δ 8.24 (s, 1H), 8.11 (m, 1H), 8.01 (s. 1H), 7.88 (d, J = 7.7, 1H), 7.67 (d, J = 7.6, 1H), 7.52 (t, J = 7.8, 1H),7.46 (b s, 5H), 7.14 (app t,
5   1H), 6.06 (s, 2H), 3.95 – 3.45 (b m, 8H); **LC/MS:** (ES+) m/z (M+H)⁺ = 581, HPLC R$_t$ = 1.463.
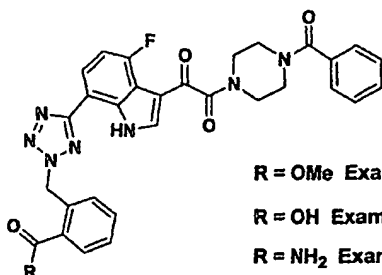
R = OMe Example 105B

R = OH Example 106B

R = NH₂ Example 107B

10
EXAMPLE 105B

¹H NMR: (CDCl₃) δ 10.95 (b s, 1H), 8.21 (d, J = 3.1, 1H), 8.11–8.10 (overlapping m, 2H), 7.58 – 7.45 (m, 2H), 7.43 (b s, 5H), 7.10 (overlapping
15   m, 2H), 6.38 (s, 2H), 3.96 – 3.50 (b m, 8H), 3.97 (s, 3H); **LC/MS:** (ES+) m/z (M+H)⁺ = 596, HPLC R$_t$ = 1.707.

EXAMPLE 106B

20   ¹H NMR: (CD₃OD) δ 8.13 (s, 1H), 8.08–8.04 (overlapping m, 2H), 7.50-7.30 (m overlapping with b s, 7H), 7.08 (d, J = 7.7 1H), 7.04 (app t, 1H), 6.34 (s, 2H), 4.00 – 3.40 (b m, 8H); **LC/MS:** (ES+) m/z (M+H)⁺ = 582, HPLC R$_t$ = 1.627.

25
EXAMPLE 107B

¹H NMR: (CD₃OD/ CDCl₃) δ 8.17 (s, 1H), 8.07 (dd, J = 8.3, 4.4, 1H), 7.60 (d, J = 7.2, 1H), 7.48–7.38 (m overlapping with b s, 7H), 7.30 (d, J = 7.2, 1H), 7.05 (b dd, 1H), 6.20 (s, 2H), 3.95 – 3.40 (b m, 8H); **LC/MS:** (ES+) m/z
30   (M+H)⁺ = 581, HPLC R$_t$ = 1.470.

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R = OMe Example 105C

R = OH Example 106C

R = NH₂ Example 107C
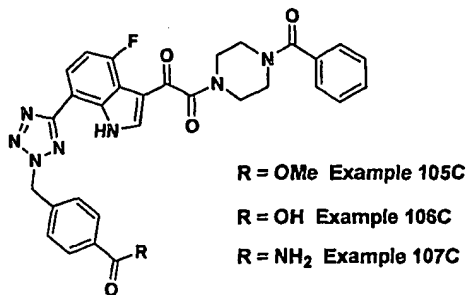
EXAMPLE 105C

5 **¹H NMR:** (CDCl₃) δ 10.95 (b s, 1H), 8.21 (d, J = 3.0, 1H), 8.10–8.07 (m overlapped d, 1H), 8.08 (d, J = 8.3, 2H), 7.49 (d, J = 8.3, 2H), 7.43 (b s, 5H), 7.10 (app t, 1H), 5.93 (s, 2H), 4.00 – 3.45 (b m, 8H), 3.92 (s, 3H); **LC/MS:** (ES+) m/z (M+H)⁺ = 596, HPLC R_t = 1.643.

10 ## EXAMPLE 106C

¹H NMR: (DMSO-d₆) δ 13.09 (b s, 1H), 12.35 (b s, 1H), 8.18 (d, J = 3.2, 1H), 8.05 (b m, 1H), 7.98 (d, J = 8.1, 2H), 7.55 (d, J = 8.1, 2H), 7.44 (b m, 5H), 7.25 (app t, 1H), 6.20 (s, 2H), 3.80 – 3.25 (b m, 8H); **LC/MS:** (ES+) m/z
15 (M+H)⁺ = 582, HPLC R_t = 1.530.

EXAMPLE 107C

¹H NMR: (CD₃OD) δ 8.23 (s, 1H), 8.09 (dd, J = 8.0, 4.3, 1H), 7.90 (d, J = 8.3,
20 2H), 7.55 (d, J = 8.3, 2H), 7.46 (b m, 5H), 7.12 (app t, 1H), 6.06 (s, 2H), 4.00 – 3.45 (b m, 8H); **LC/MS:** (ES+) m/z (M+H)⁺ = 581, HPLC R_t = 1.380.

Example 108

Example 109

25   The products of **Example 108** and **Example 109** were prepared analogously to the product of **Example 22**.

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EXAMPLE 108

¹H NMR: (CDCl₃) δ 10.89 (b s, 1H), 8.24 (d, *J* = 3.1, 1H), 8.17 (dd, *J* = 4.4,
8.3, 1H), 7.43 (b s, 5H), 7.14 (app t, 1H), 6.59 (s, 2H), 4.00 – 3.45 (b m, 8H),
5   2.21 (s, 3H); **LC/MS:** (ES+) m/z (M+H)⁺ = 520, HPLC R$_t$ = 1.497.

EXAMPLE 109

¹H NMR: (CDCl₃) δ 10.90 (b s, 1H), 8.24 (d, *J* = 3.1, 1H), 8.17 (dd, *J* = 4.3,
10   8.3, 1H), 7.43 (b s, 5H), 7.14 (app t, 1H), 6.59 (s, 2H), 4.00 – 3.45 (b m, 8H),
1.24 (s, 9H); **LC/MS:** (ES+) m/z (M+H)⁺ = 562, HPLC R$_t$ = 1.683.

Example 74 → Example 110A → Example 111
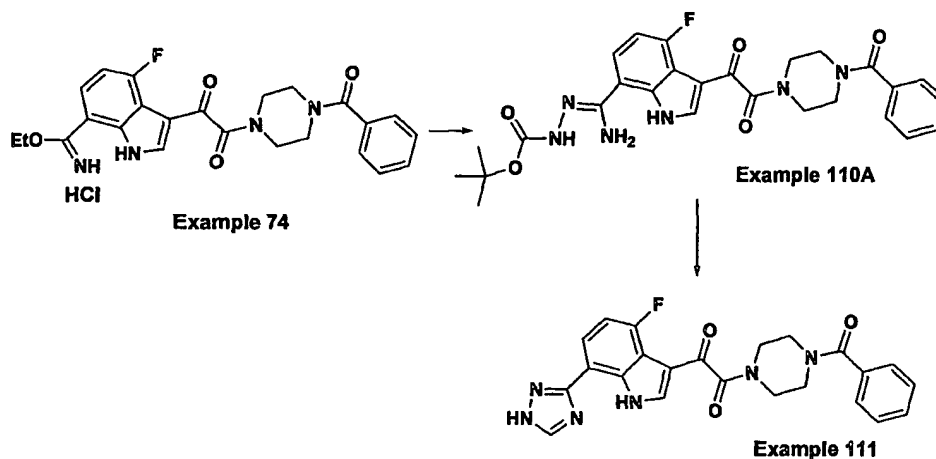
15   **EXAMPLE 110A**

To compound from **Example 74** (crude, 0.495 mmol) in EtOH (2 ml, 200
proof, anhydrous, 99.5+% from Aldrich) was added *tert*-butyl carbazate (196
mg, 1.485 mmol). The resulting mixture was stirred at room temperature for 3
20   hours. The reaction mixture was then added MeOH (4 ml) and purified by
reverse phase preparative HPLC using the method: Start %B = 25, Final %B
= 90, Gradient time = 15 min, Flow Rate = 25 ml/min, Column: YMC C18 S5
20 x 100mm, Fraction Collection: 6.61 – 7.34 min.; **¹H NMR:** (CD₃OD) δ 8.33
(s, 1H), 7.65 (app dd, *J* = 7.8, 3.9, 1H), 7.47 (b s, 5H), 7.21 (app t, *J* = 9.3,
25   1H), 3.97 – 3.40 (b m, 8H), 1.56 (s, 9H); **LC/MS:** (ES+) m/z (M+H)⁺ = 537,
HPLC R$_t$ = 1.170 min.   Fraction Collection of 11.62–12.43 min. gave

compound of **Example 110B**. LC/MS: (ES+) m/z (M+H)$^+$ = 652, HPLC R$_t$ = 1.417.
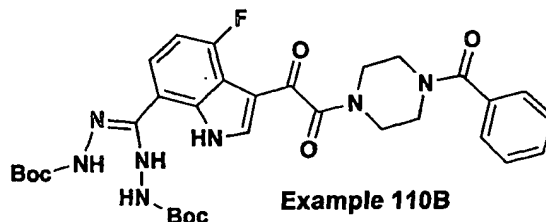
Example 110B

EXAMPLE 111

To the compound of **Example 110A** (16 mg, 0.030 mmol) was charged triethylorthoformate (1 ml). The resulting mixture was heated at 110°C for 16 hours. After cooled to room temperature, the reaction mixture was dissolved in MeOH (2 ml) and purified by reverse phase preparative HPLC using the method: Start %B = 15, Final %B = 75, Gradient time = 16 min, Flow Rate = 25 ml/min, Column: YMC C18 S5 20 x 100mm, Fraction Collection: 10.72 – 11.52 min.; ^{1}H NMR: (CDCl$_3$) δ 11.16 (b s, 1H), 8.39 (s, 1H), 8.12 (s, 1H), 7.87 (app dd, J = 8.0, 4.1, 1H), 7.44 (b s, 5H), 7.01 (app t, J = 9.4, 1H), 3.98 – 3.51 (b, m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 447, HPLC R$_t$ = 1.257 min.

Alternatively, compound of Example 111 was prepared directly from compound of Example 74 by the following procedure: To a solution of compound of Example 74 (100 mg, 0.205 mmol) in EtOH (2 ml) was charged N,N-diisopropylethylamine (0.1 ml, 0.57 mmol) and formic hydrazide (57 mg, 0.95 mmol). The resulting mixture was heated at 60°C for 16 hours. After cooled to room temperature, the reaction mixture was dissolved in MeOH (4 ml) and purified by preparative reverse phase HPLC using the same method as above.

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EXAMPLE 112
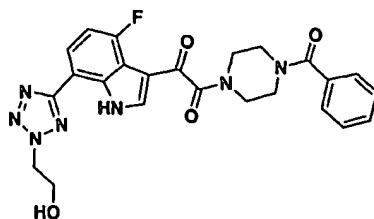
5   Compound of Example 112   was prepared by the reduction of
compound of Example 22 using NaBH$_4$ in EtOH/THF (1:2) at rt. ^{1}H NMR:
(CDCl$_3$) δ 10.30 9b s, 1H), 8.01 (b m, 1H), 7.47-7.32 (b m, 6H), 6.97 (b m,
1H), 5.84 (b s, 1H), 4.88 (t, J = 5.0, 2H), 4.29 (t, J = 5.0, 2H),4.00 – 3.00 (b
m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 492, HPLC R$_t$ = 1.250.

10

EXAMPLE 113
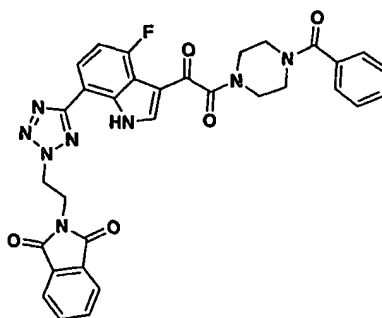
15   Compound of Example 113 was prepared analogously to compound of
Example 22. ^{1}H NMR: (CDCl$_3$) δ 10.96 (b s, 1H), 8.21 (d, J = 3.2, 1H), 7.97
(dd, J = 8.4, 4.4, 1H), 7.85–7.80 (overlapping m, 2H), 7.76–7.72 (overlapping
m, 2H), 7.43 (b s, 5H), 7.06 (dd, J =10.2, 8.4, 1H), 5.08 (t, J = 5.6, 2H), 4.40
(t, J = 5.6, 2H), 4.05–3.40 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 621, HPLC
20   R$_t$ = 1.557.

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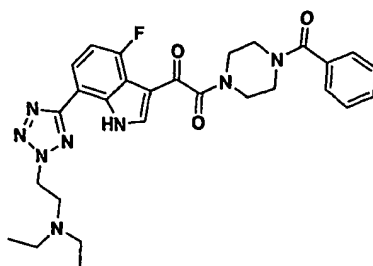
EXAMPLE 114

5   Compound of Example 114 was prepared analogously to compound of Example 22. **¹H NMR:** (CD₃OD) δ 8.25 (s, 1H), 8.13 (b dd, 1H), 7.47 (b s, 5H), 7.16 (b app t, 1H), 4.87 (buried t, 2H), 4.00–3.45 (b m, 8H), 3.20 (t, J = 6.4, 2H), 2.62 (q, J = 7.1, 4H), 1.00 (t, J = 7.1, 6H); **LC/MS:** (ES+) m/z $(M+H)^+$ = 547, HPLC R_t = 1.143.

10

EXAMPLE 115
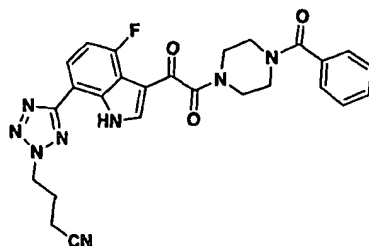
15   Compound of Example 115 was prepared analogously to compound of Example 22. **¹H NMR:** (CDCl₃) δ 10.98 (b s, 1H), 8.22 (d, J = 3.0, 1H), 8.09 (dd, J = 8.3, 4.4, 1H), 7.43 (b s, 5H), 7.13 (app t, 1H), 4.92 (t, J = 6.4, 2H), 4.00–3.40 (b m, 8H), 2.59–2.48 (overlapping m, 4H); **LC/MS:** (ES+) m/z $(M+H)^+$ = 515, HPLC R_t = 1.350.

20

EXAMPLE 116
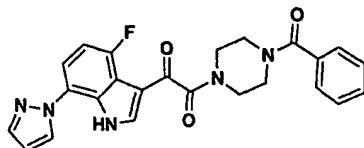
25   A mixture of intermediate 34a (c.a. 0.149 mmol) and the hydrochloride salt of intermediate 19 (52.0 mg, 0.229 mmol) in THF (1.0 ml) was added NMM (0.1 ml, 0.910 mmol), and the resulting mixture stirred at rt for 22 h. The mixture

was then added intermediate 19 (43.0 mg, 0.190 mmol), DMAP (30.4 mg, 0.249 mmol), EDC (48.0 mg, 0.250 mmol), NMM (0.1 ml, 0.910 mmol), and DMF (1.5 ml), and stirred for a further 24 h to complete the reaction. The volatile was then evaporated to give a residue, which was diluted with excess

5   H_2O and acidified to pH ~1 with HCl (1 N, aq.). The precipitates were filtered and washed with H_2O (2 ml) and dried. The crude solid was purified by preparative TLC (5% $MeOH/CH_2Cl_2$, two of 500 μm x 20 cm x 20 cm plates) to give the product of Example 116. ^{1}H NMR: ($CDCl_3$) δ 11.47 (b s, 1H), 8.15 (d, J = 3.1, 1H), 8.09 (d, J = 2.5, 1H), 7.80 (d, J = 1.8, 1H), 7.43 (b s, 5H),

10 7.33 (dd, J = 8.6, 3.5, 1H), 7.01 (app t, 1H), 6.55 (t, J = 2.2, 1H), 4.10–3.40 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 446, HPLC R$_t$ = 1.363.

EXAMPLE 117

15
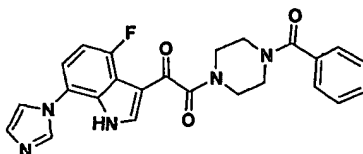
Compound of Example 117 was prepared analogously to compound of Example 116, except that only DMF was used as the solvent and the crude material was purified by reverse phase preparative HPLC. ^{1}H NMR: (CD_3OD)

20 δ 9.45 (s, 1H), 8.28 (s, 1H), 7.98 (s,1H), 7.86 (s, 1H), 7.54 (dd, J = 8.4, 3.4, 1H), 7.46 (b s, 5H), 7.18 (app t, 1H), 4.00–3.45 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 446, HPLC R$_t$ = 0.967.

EXAMPLE 118

25
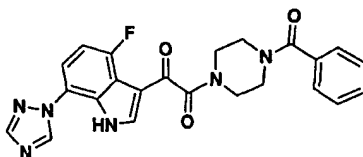
Compound of Example 118 was prepared analogously to compound of Example 116, except that only DMF was used as the solvent. ^{1}H NMR:

30 ($CDCl_3$) δ 10.95 (b s, 1H), 8.76 (s, 1H), 8.24 (s, 1H), 8.19 (d, J = 3.1, 1H),

7.49–7.43 (dd overlapped with b s, 6H), 7.08 (app t, 1H), 4.00–3.40 (b m, 8H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 447, HPLC R$_t$ = 1.187.

Example 119

5
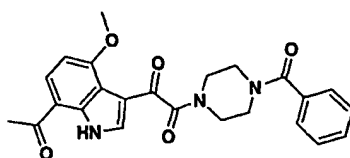
A mixture of intermediate 38 (*c.a.* 0.109 mmol) and the hydrochloride salt of intermediate 19 (38.0 mg, 0.168 mmol) in DMF (2.0 ml) was added DMAP

10   (25.0 mg, 0.205 mmol), EDC (38.3 mg, 0.2 mmol) and NMM (55 µl, 0.5 mmol), and the resulting mixture stirred at rt for 22 h. The mixture was then added another amount of the amine (38.0 mg, 0.168 mmol) followed by DMF (1.5 ml), and stirred for 24 h. After which time, DMAP (25.0 mg, 0.205 mmol), EDC (38.3 mg, 0.2 mmol) and NMM (55 µl, 0.5 mmol) were added

15   again to the reaction mixture, which was then stirred for a further 24 h to complete the reaction. The volatile was then evaporated under high vacuum to give a residue, which was diluted with H$_2$O (~ 15 ml) and acidified to pH ~1 with HCl (1 *N*, aq.). The resulting mixture was extracted with EtOAc (40 ml), and the organic extract washed with HCl (25 ml, 1 *N*, aq.) and evaporated to

20   give a crude product. The crude material was purified by preparative TLC (5% MeOH/CH$_2$Cl$_2$, 500 µm x 20 cm x 20 cm plates) to give the product as a yellow glass, which was then treated with MeOH (2 x 0.5 ml) and the methanolic layer removed by pipet to give the solid of Example 119. ^{1}H NMR: (CDCl$_3$) δ 8.07 (s, 1H), 7.86 (d, *J* = 8.4, 1H), 7.43 (b s, 5H), 6.73 (d, *J* = 8.4,

25   1H), 4.04 (s, 3H), 4.00–3.40 (b s, 8H), 2.67 (s, 3H); LC/MS: (ES+) m/z (M+H)$^+$ = 456, HPLC R$_t$ = 1.227.

Example 120
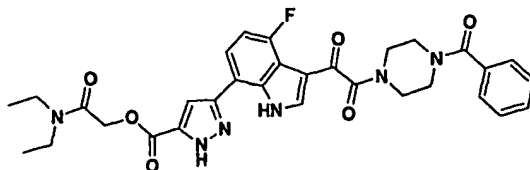
30

To a mixture of the compound prepared in Example 88 (13.7 mg, 0.028 mmol) and 2-chloro-*N*,*N*-diethylacetamide (5.0 mg, 0.033 mmol) in DMF (1.0 ml) was added triethylamine (10 µl, 0.036 mmol), and the resulting mixture stirred at rt for 24 h. NaI (one pipet tip), 2-chloro-*N*,*N*-

5 diethylacetamide (5.0 mg, 0.033 mmol) and triethylamine (10 µl, 0.036 mmol) were then added successively to the reaction mixture. After stirring at rt for another 21 h, the three reagents were added again in the same order to the reaction mixture. The resulting mixture was stirred for another 20 h to complete the reaction and then evaporated under high vacuum to give a

10 residue, which was purified by preparative TLC (5% MeOH/CH$_2$Cl$_2$, 1 x 500 µm x 20 cm x 20 cm plate) to give the product as a white solid. **^{1}H NMR:** (CDCl$_3$) δ 12.35 (b s, 1H), 11.26, (b s, 1H), 8.14 (s, 1H), 7.43 (b s, 6H), 6.97 (app t, 1H), 5.02 (s, 2H), 4.00 – 3.40 (b m, 8H), 3.46 (q, *J* = 7.1, 2H), 3.33 (q, *J* = 7.1, 2H), 1.29 (t, *J* = 7.1, 3H), 1.18 (t, *J* = 7.1, 3H); **LC/MS:** (ES+) m/z

15 (M+H)$^+$ = 603, HPLC R$_t$ = 1.530.

Example 121

20
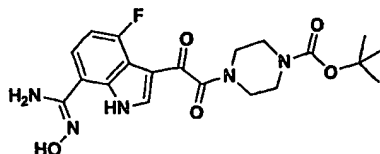
Compound of Example 121 was prepared from intermediate 39 analogously to Example 27, and purified by preparative TLC (10% MeOH/CH$_2$Cl$_2$, 500 µm x 20 cm x 20 cm plates). **^{1}H NMR:** (CD$_3$OD) δ 8.12 (s, 1H), 7.59 (dd, *J* = 8.4, 4.3, 1H), 7.02 (dd, *J* = 10.5, 8.4, 1H), 3.72 (b m, 2H),

25 3.57 (b s, 2H), 3.46 (b s, 4H), 1.46 (s, 9H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 434, HPLC R$_t$ = 1.137.

Example 122

30
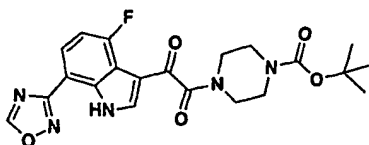
Compound of Example 122 was prepared from compound of Example 121 analogously to Example 79, and purified by preparative TLC (5%

176

MeOH/CH$_2$Cl$_2$, 500 μm x 20 cm x 20 cm plate). ^{1}H NMR: (CDCl$_3$) δ 8.87 (s, 1H), 8.20 (d, J = 3.1, 1H), 8.15 (dd, J = 8.4, 4.5, 1H), 7.15 (dd, J = 10.2, 8.4, 1H), 3.74 (app t, 2H), 3.57 (app t, 2H), 3.51 (m, 4H), 1.48 (s, 9H); **LC/MS:** (ES+) m/z (M+Na)$^+$ = 466, HPLC R$_t$ = 1.537.

5

EXAMPLE 123
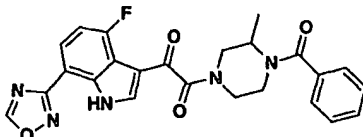
10   To a mixture of intermediate 50 (100 mg, 0.493 mmol) in DMF (2.0 ml) was added 2-methylpiperazine (54.3 mg, 0.542 mmol), and NMM (60 μl, 0.546 mmol), and the resulting mixture stirred at rt for 20 h. After which time, LC/MS analysis showed the formation of a monoamide and the hydrolyzed side product of intermediate 50 (ketoacid). The reaction mixture was then 15 added 2-methylpiperazine (54.3 mg, 0.542 mmol), EDC (104 mg, 0.542 mmol), DMAP (66.3 mg, 0.543 mmol) and NMM (120 μl, 1.09 mmol) and stirred for 21 h to complete the formation of the monoamide. Benzoic acid (66.0 mg, 0.540 mmol), followed by EDC (104 mg, 0.542 mmol), DMAP (66.3 mg, 0.543 mmol) and NMM (120 μl, 1.09 mmol) were added to the reaction 20 mixture, which was stirred for another 27 h. The mixture was diluted with water (about 10 ml) and acidified with HCl (1 N, aq.) to induce precipitation. The precipitates were filtered, washed HCl (3 x 2 ml, 1 N, aq.) and dried. The crude was purified by preparative TLC (5% MeOH/CH$_2$Cl$_2$, 500 μm x 20 cm x 20 cm plate) to give the product as a white solid. The position of the 25 piperazine methyl group was supported by H-H NOESY studies. ^{1}H NMR: (a ~1:1 mixture of 2 conformational isomers) (CDCl$_3$) δ 10.60 (b s, 1H), 8.86 (s, 1H), 8.21 (app t, 1H), 8.15 (m, 1H), 7.42 (b m, 5H), 7.14 (m, 1H), 4.65, 4.47, 3.95 and 3.76 (app b d, 4H), 3.50–2.90 (overlapping b m, 3H), 1.37 and 1.32 (d, J = 6.7, 3H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 462, HPLC R$_t$ = 1.407.

177

EXAMPLE 124
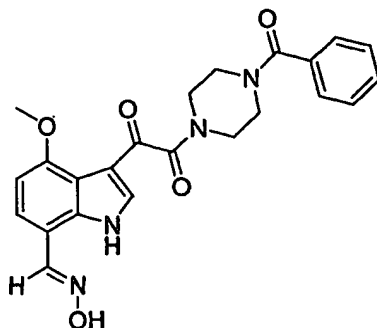
5   To the aldehyde intermediate 42 (20 mg, 0.048 mmol) in EtOH (2 ml) at rt.
    was added hydroxyamine (0.5 ml, 50% in H_2O), and the mixture stirred
    overnight. The crude mixture was then purified by reverse phase preparative
    HPLC to give compound of Example 124 (15.9 mg, 77%). ^{1}H NMR: (CD_3OD)
    δ 8.25 (s, 1H), 8.11 (s, 1H), 7.38-7.57 (b s, 5H), 7.27 (d, J = 8.2 Hz, 1H), 6.79
10 (d, J = 8.2 Hz, 1H), 3.93 (s, 3H), 3.38-3.95 (m, 8H); LC/MS: (ES+) m/z
    $(M+H)^+$ = 435, HPLC (YMC C18 S7 3 x 50 mm, Flow Rate 4 ml/min, Gradient
    Time 2 min) R_t = 1.263.

EXAMPLE 125

15
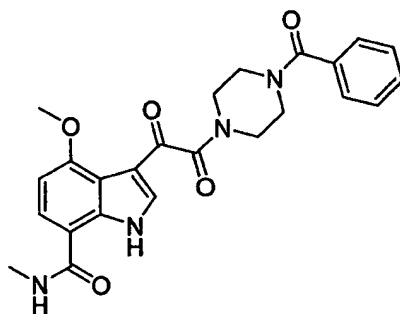
    To the ester intermediate 45 (17 mg, 0.056 mmol) in EtOH (5ml) was added
    10 N NaOH (0.028 ml, 0.28 mmol), and the reaction mixture stirred for 28 hr
20 at rt. The solvent was removed *in vacuo* and the residue dried overnight
    under high vacuum. The crude sodium salt in DMF (5ml) at rt., after adding
    N,N-diisopropylethylamine (36.2 mg, 0.049 ml, 0.28 mmol) and 3-
    (diethoxyphosphoryloxy)-1,2,3-benzotriazo-4(3*H*)-one (18.4 mg, 0062 mmol),
    was treated with the benzoylpiperazine hydrochloride salt (16.5 mg, 0.073
25 mmol) The reaction mixture was then stirred at rt. for 48 hr before the solvent

partially removed *in vacuo*. The crude mixture was dissolved in MeOH and purified by reverse phase preparative HPLC to afford compound of Example

125 (10 mg, 40% two steps). ^{1}H NMR: (300 MHz, CD$_3$OD) δ 8.13 (s, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.46 (b s, 5H), 6.81 (d, J = 8.4 Hz, 1H), 3.78 (s, 3H),

5   3.20-3.98 (m, 8H), 2.94 (s, 3H); LC/MS: (ES+) m/z (M+H)$^+$ = 449, HPLC (YMC C18 S7 3 x 50 mm, Flow Rate 4 ml/min, Gradient Time 2 min) R$_t$ = 1.180.

EXAMPLE 126

10
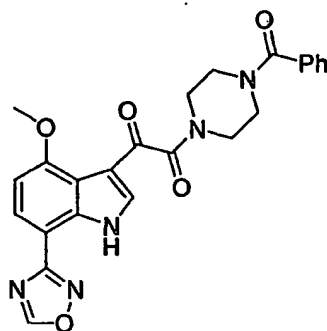
Intermediate 46 (120 mg, 0.288 mmol) was dissolved in hot EtOH (6 ml). After cooling to rt., the mixture was added dropwise NH$_2$OH (0.5 ml, 50% in

15   H$_2$O) and then stirred at rt. for 3 hr. The crude material was purified by reverse phase preparative HPLC to afford a 4:1 mixture (72 mg) of the desired hydroxyaminidine (I) and its oxime side product (II), which was submitted to the cyclization reaction without further purification. LC/MS: (ES+) m/z (M+H)$^+$ = 450 (I) and 465 (II), HPLC (YMC C18 S7 3 x 50 mm,

20   Flow Rate 4 ml/min, Gradient Time 2 min) R$_t$ = 0.890 (I and II).

To the above 4:1 mixture (72 mg) of I and II in a 10 ml-flask was added anhydrous triethyl orthoformate (4 ml) and the resulting mixture stirred at 110°C for 3 hr. After cooling to rt., the crude mixture was purified by reverse phase preparative HPLC to give compound of Example 126 (15 mg). The

25   mixture was further purified by preparative TLC (5% MeOH/CH$_2$Cl$_2$, one 500 μm x 20 cm x 20 cm plate) to remove the side product. ^{1}H NMR: (CD$_3$OD) δ 9.32 (s, 1H), 8.17 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.47 (b s, 5H), 6.95 (d, J = 8.4 Hz, 1H), 4.07-3.42 (m, 8 H), 4.00 (s, 3H); LC/MS: (ES+) m/z (M+H)$^+$ = 460, HPLC (YMC C18 S7 3 x 50 mm, Flow Rate 4 ml/min, Gradient Time 3

30   min) R$_t$ = 1.770.

179

RCONHNH$_2$
^{i}Pr$_2$NEt, EtOH

Example 74

R =

Example 127   Example 128   Example 129   Example 130   Example 131
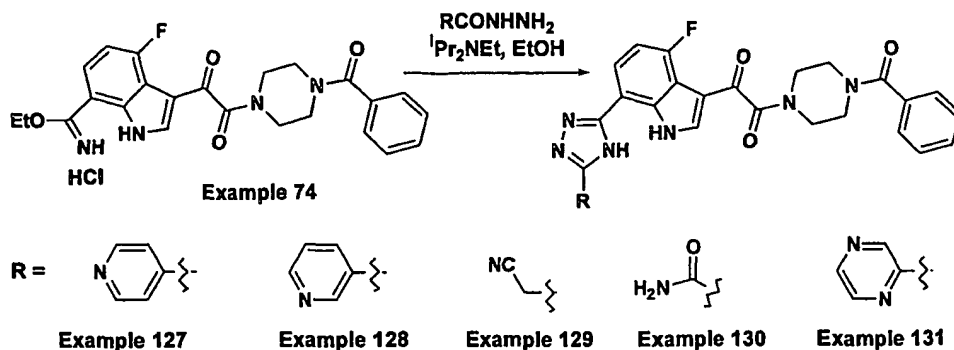
EXAMPLE 127

Compound of Example 127 was prepared in the same manner as the alternative method of Example 111. Purification was performed preparative by revers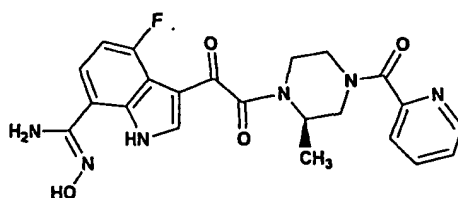e phase preparative HPLC using the method: Start %B = 30, Final %B = 90, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100 mm, Fraction Collection: 7.16 – 7.62 min. ^{1}H NMR: (CD$_3$OD) δ 8.84 (overlapping doublets, 4H), 8.31 (b s, 1H), 7.96 (b s,1H), 7.47 (b s, 5H), 7.17 (app t, J = 9.2, 1H), 3.97 – 3.38 (b, m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 524, HPLC R$_t$ = 1.717.

EXAMPLE 128

Compound of Example 128 was prepared in the same manner as compound of Example 127. ^{1}H NMR: (CD$_3$OD) δ 9.54 (b m, 1H), 9.08 (b m, 1H), 8.81 (b s,1H), 8.30 (s, 1H), 7.98 (b m, 2H), 7.47 (b s, 5H), 7.17 (app t, J = 8.7, 1H), 3.98 – 3.44 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 524, HPLC R$_t$ = 1.763.

EXAMPLE 129

Compound of Example 129 was prepared in the same manner as compound of Example 127. Purification was performed by preparative reverse phase HPLC using the method: Start %B = 30, Final %B = 90, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100 mm, Fraction

Collection: 7.58 – 8.03 min. ^{1}H NMR: (CD$_3$OD) δ 8.25 (s, 1H), 7.92 (b s, 1H), 7.46 (b s, 5H), 7.12 (app t, J = 8.5, 1H), 4.20 (s, 2H), 3.97 – 3.44 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 524, HPLC R$_t$ = 1.753.

EXAMPLE 130

Compound of Example 130 was prepared in the same manner as compound of Example 127, except that the reaction temperature was 100 °C. Purification was performed by preparative reverse phase HPLC using the method: Start %B = 30, Final %B = 90, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100mm, Fraction Collection: 7.63 – 8.08 min. ^{1}H NMR: (DMSO-d_6) δ 12.50 (s, 1H), 8.67 (s, 1H), 8.20 (d, J = 3.0, 1H), 8.03 (app dd, J = 8.0, 4.3, 1H), 7.44 (b s, 5H), 7.21 (app t, J = 9.1, 1H), 3.91 – 3.31 (overlapping with broad water peak, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 490, HPLC R$_t$ = 1.777.

EXAMPLE 131

Compound of Example 131 was prepared (using hydrazide intermediate 47) in the same manner as compound of Example 127, except that the reaction temperature was 78 °C. ^{1}H NMR: (CD$_3$OD) δ 9.59 (s, 1H), 8.74 (overlapping doublets, 2H), 8.29 (s, 1H), 8.07 (b s, 1H), 7.47 (b s, 5H), 7.14 (app t, J = 8.4, 1H), 3.99 – 3.44 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 525, HPLC R$_t$ = 1.447.

EXAMPLE 132

Example 110B   Example 132
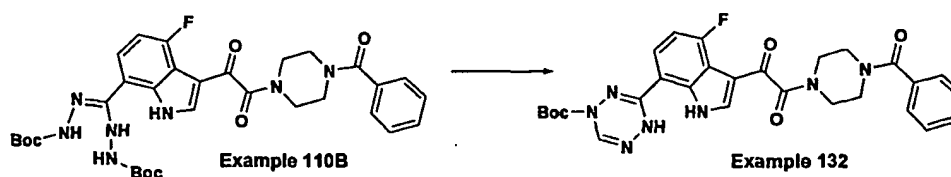
To compound of Example 110B (crude, 20 mg, 0.031 mmol) was charged triethylorthoformate (1 ml). The resulting mixture was heated at 110°C for 16 hours. After cooled to room temperature, the mixture was dissolved in MeOH (2 ml) and purified by preparative reverse phase HPLC using the method: Start %B = 30, Final %B = 80, Gradient time = 16 min, Flow Rate = 25

ml/min, Column : YMC C18 S5 20 x 100 mm, Fraction Collection: 10.50 – 11.08 min. ¹H NMR: (CD₃OD) δ 8.81 (s, 1H), 8.19 (s, 1H), 7.77 (b, s, 1H), 7.46 (b s, 5H), 7.15 (app t, J = 8.9, 1H), 3.88 – 3.44 (b m, 8H), 1.37 (b s, 9H); LC/MS: (ES+) m/z (M+H)⁺ = 562, HPLC R$_t$ = 1.370.

EXAMPLE 133

Example 92 → Example 133
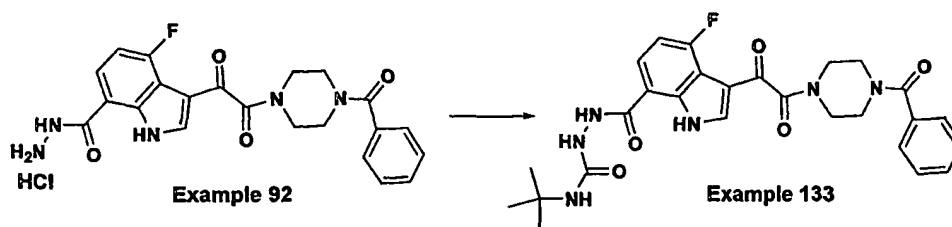
To a solution of compound of Example 92 (100 mg, 0.211 mmol) in EtOH (2 ml), was added N,N-diisopropylethylamine (0.1 ml) and tert-butylisocyanate (50 µl, 0.438 mmol). The reaction mixture was stirred at room temperature for 16 hours and then filtered. The filtrate wa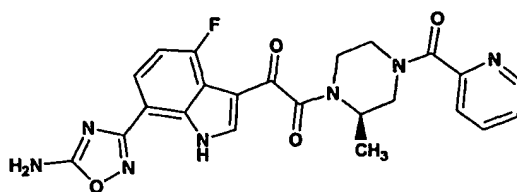s purified by preparative reverse phase HPLC using the method: Start %B = 30, Final %B = 100, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100 mm, Fraction Collection: 7.79 – 8.24 min. ¹H NMR: (CD₃OD) δ 8.19 (s, 1H), 7.82 (app dd, J = 8.1, 4.2, 1H), 7.46 (b s, 5H), 7.03 (app t, J = 9.0, 1H), 3.99 – 3.43 (b m, 8H), 1.35 (b, s, 9H); LC/MS: (ES+) m/z (M+H)⁺ = 537, HPLC R$_t$ = 1.790.
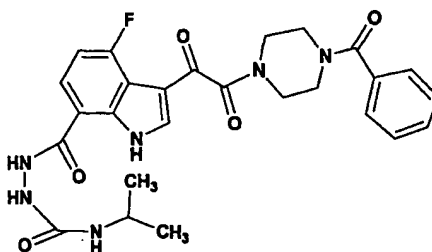
EXAMPLE 134

Compound of Example 134 was prepared in the same manner as compound of Example 133. Purification was performed by reverse phase preparative HPLC using the method: Start %B = 30, Final %B = 80, Gradient time = 12 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100mm, Fraction

Collection: 6.74 – 7.07 min. ^{1}H NMR (CD$_3$OD) δ 8.13 (s, 1H), 7.76 (b m, 1H), 7.43 (b s, 5H), 6.99 (app t, J = 8.8, 1H), 3.88 (app, dd, overlapping with b m, J = 13.0, 6.5, 1H) 3.95 – 3.49 (b m, 8H), 1.13 (d, J = 6.5, 6H); **LC/MS** (ES+) m/z (M+H)$^+$ = 523, HPLC R$_t$ = 1.607.

5

EXAMPLE 135
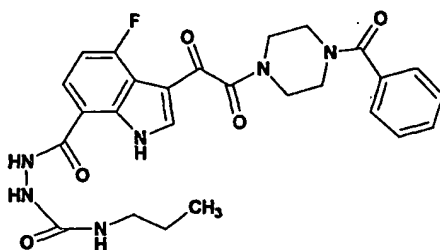
10　Compound of Example 135 was prepared in the same manner as compound of Example 133. Purification was performed by reverse phase preparative HPLC using the method: Start %B = 30, Final %B = 95, Gradient time = 16 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100mm, Fraction Collection: 6.57 – 7.50 min. ^{1}H NMR (CD$_3$OD) δ 8.18 (s, 1H), 7.86 (b m, 1H),
15　7.46 (b s, 5H), 7.04 (app, t, J = 9.2, 1H), 3.97 – 3.38 (b m, 8H), 3.14 (app dd, J = 13.1, 5.5, 2H), 1.53 (m, 2H), 0.92 (t, J = 7.4, 3H); **LC/MS** (ES+) m/z (M+H)$^+$ = 523, HPLC R$_t$ = 1.593.

Example 97

R = NH$_2$　　Example 136

MeNH　　Example 137

Me$_2$N　　Example 138
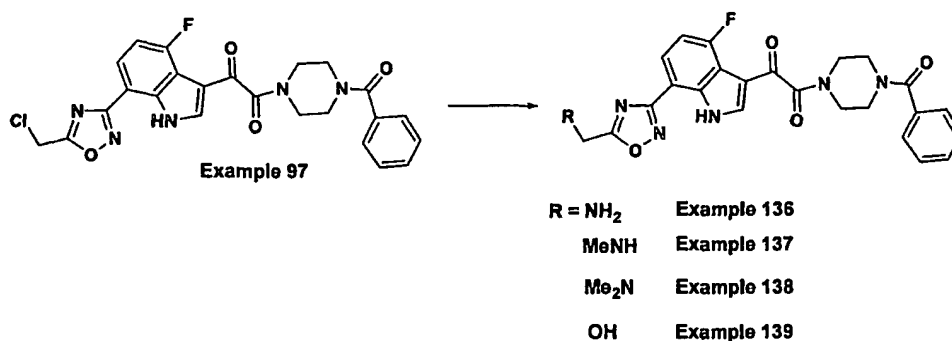
OH　　Example 139

20

EXAMPLE 136

To a solution of compound of Example 97 (13 mg, 0.026 mmol) in THF (2 ml) in a reusable sealed tube at -78°C was bubbled ammonia for one hour. The
25　tube was tightly sealed, and the reaction mixture was stirred at room

temperature for 16 hours. After removal of most of the solvent, the resulting residue was added MeOH (2 ml) and purified by preparative reverse phase HPLC using the method: Start %B = 10, Final %B = 80, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100 mm, Fraction

5   Collection: 12.98 – 13.48 min. **¹H NMR:** (DMSO-d_6) δ 12.33 (s, 1H), 8.85 (s, 2H), 8.22 (d, J = 3.2, 1H), 8.05 (app dd, J = 8.2, 4.4, 1H), 7.44 (b s, 5H), 7.31 (app t, J = 9.2, 1H), 4.69 (s, 2H), 3.87 – 3.30 (b, m, 8H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 476, HPLC R$_t$ = 1.117.

10   **EXAMPLE 137**

To compound of Example 97 (30 mg, 0.060 mmol) was added an aqueous solution of methylamine (1 ml, 40 wt. %). The reaction mixture was stirred at room temperature for 16 hours. After removal of most of the solvent, the

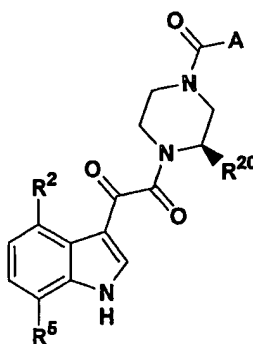15   resulting residue was added MeOH (4 ml) and purified by preparative reverse phase HPLC using the method: Start %B = 10, Final %B = 80, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100 mm, Fraction Collection: 9.67 – 10.18 min. **¹H NMR:** (CD$_3$OD) δ 8.25 (s, 1H), 8.15 (app dd, J = 8.2, 4.3, 1H), 7.46 (b s, 5H), 7.18 (app t, J = 9.0, 1H), 4.80 (s,

20   2H), 3.99 – 3.43 (b, m, 8H), 2.98 (s, 3H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 491, HPLC R$_t$ = 1.120.

                                           EXAMPLE 138

25   To compound Example 97 (10 mg, 0.020 mmol) was added an aqueous solution of dimethylamine (0.5 ml, 40 wt. %). The reaction mixture was stirred at room temperature for 16 hours. After removal of most of the solvent, the resulting residue was added MeOH (4 ml) and purified by preparative reverse phase HPLC using the method: Start %B = 10, Final %B = 80, Gradient time

30   = 10 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100 mm, Fraction Collection: 7.37 – 7.83 min. **¹H NMR:** (CD$_3$OD) δ 8.24 (s, 1H), 8.16 (app dd, J = 8.1, 4.4, 1H), 7.47 (b s, 5H), 7.19 (app t, J = 9.2, 1H), 4.96 (s,

184

2H), 3.85 – 3.43 (b, m, 8H), 3.16 (s, 6H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 505, HPLC R$_t$ = 1.110.

EXAMPLE 139

5

To a solution of compound Example 97 (10 mg, 0.020 mmol) in MeOH (0.5 ml) was added an aqueous solution of NaOH (0.2 ml, 1 *N*). The reaction mixture was stirred at room temperature for 4 hours. After removal of most of the solvent, the resulting residue was added MeOH (2 ml) and purified by

10 preparative reverse phase HPLC using the method: Start %B = 20, Final %B = 100, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100 mm, Fraction Collection: 10.26 – 10.76 min. ^{1}**H NMR:** (CD$_3$OD) δ 8.20 (s, 1H), 8.09 (app dd, J = 8.0, 4.4, 1H), 7.46 (b s, 5H), 7.03 (app t, J = 9.0, 1H), 4.83 (s, 2H), 3.99 – 3.45 (b m, 8H); **LC/MS:** (ES+) m/z

15 (M+H)$^+$ = 478, HPLC R$_t$ = 1.983.

EXAMPLE 140

Example 81 → Example 140
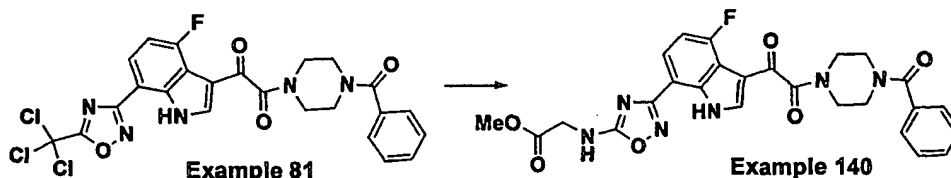
20

To a solution of compound Example 81 (30 mg, 0.053 mmol) in THF (1 ml) was added glycine methyl ester hydrochloride (33 mg, 0.265 mmol) and Hunig's base (0.3 ml). The reaction mixture was stirred at room temperature for 16 hours. After removal of most of the solvent, the residue was added

25 MeOH (4 ml) and purified by preparative reverse phase HPLC using the method: Start %B = 20, Final %B = 90, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100 mm, Fraction Collection: 10.45 – 11.02 min. ^{1}**H NMR:** (CDCl$_3$, two isomers) δ 10.60 (b s, 1H), 8.20 & 8.15 (d, J = 2.8, 1H), 8.09 & 7.92 (app dd, J = 8.2, 4.3, 1H), 7.43 (b s, 5H), 7.12 & 7.06

30 (app t, J = 9.2, 1H), 7.84 & 6.25 (b s, 1H), 4.31 (overlapping doublets, J = 4.6, 2H), 3.98 – 3.49 (b m, 8H), 3.86 (s, overlapping with b m, 3H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 535 HPLC R$_t$ = 1.397.

185
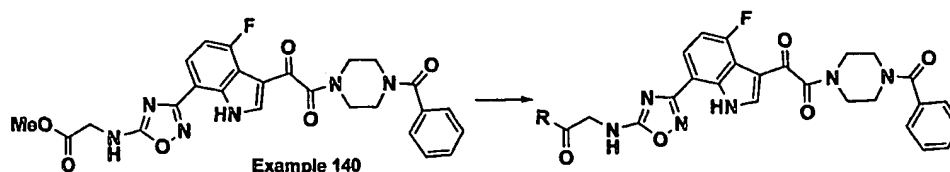
Example 140

R = OH   Example 141
NH$_2$ Example 142
MeNH   Example 143

EXAMPLE 141

To a solution of compound of Example 140 (16 mg, 0.03mmol) in MeOH (0.5 ml) was added an aqueous solution of NaOH (0.1 ml, 0.1 mmol, 1 *N*). The reaction mixture was stirred at room temperature for 4 hours. After adjusting the pH to about 2 using hydrochloric acid (1 *N*), the reaction mixture was added MeOH (2 ml) and purified by preparative reverse phase HPLC using the method: Start %B = 20, Final %B = 90, Gradient time = 20 min, Flow Rate = 35 ml/min, Column : YMC C18 S5 30 x 100 mm, Fraction Collection: 13.00 – 13.52 min. ^{1}H NMR: (CD$_3$OD) δ 8.18 (s, 1H), 7.95 (app dd, *J* = 8.1, 4.4, 1H), 7.46 (b s, 5H), 7.08 (app t, *J* = 9.2, 1H), 4.23 (s, 2H), 3.98 – 3.45 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 521, HPLC R$_t$ = 1.330.

EXAMPLE 142

To a solution of compound of Example 140 (15 mg, 0.028 mmol) in THF (1 ml) in a reusable sealed tube at -78°C was bubbled ammonia for one hour. The tube was tightly sealed, and the reaction mixture stirred at room temperature for 16 hours. After removal of most of the solvent, the resulting residue was added MeOH (2 ml) and purified by preparative reverse phase HPLC to afford the product as a TFA salt. HPLC method: Start %B = 25, Final %B = 80, Gradient time = 20 min, Flow Rate = 35 ml/min, Column : YMC C18 S5 30 x 100 mm, Fraction Collection: 11.77 – 12.29 min. ^{1}H NMR: (CD$_3$OD) δ 8.19 (s, 1H), 7.97 (app dd, *J* = 8.0, 4.0, 1H), 7.46 (b s, 5H), 7.10 (app t, *J* = 9.2, 1H), 4.15 (s, 2H), 3.98 – 3.44 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 520, HPLC R$_t$ = 1.217.

186

EXAMPLE 143

To compound of Example 140 (20 mg, 0.037 mmol) was added an aqueous solution of methylamine (0.5 ml, 40 wt. %). The resulting mixture was stirred
5   at room temperature for 16 hours. After removal of most of the solvent, the resulting residue was added MeOH (2 ml) an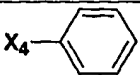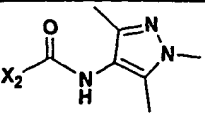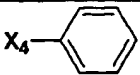d purified by preparative reverse phase HPLC using the method: Start %B = 20, Final %B = 85, Gradient time = 15 min, Flow Rate = 35 ml/min, Column : YMC C18 S5 30 x 100 mm, Fraction Collection: 10.62– 11.14 min. ^{1}H NMR: (CD$_3$OD) δ 8.19 (s, 1H),
10   7.96 (app dd, J = 8.0, 4.3, 1H), 7.46 (b s, 5H), 7.10 (app t, J = 9.2, 1H), 4.13 (s, 2H), 3.86 – 3.45 (b m, 8H), 2.78 (s, 3H); LC/MS: (ES+) m/z (M+H)$^+$ = 478, HPLC R$_t$ = 1.983.

EXAMPLE 144
15

Example 111   Example 144
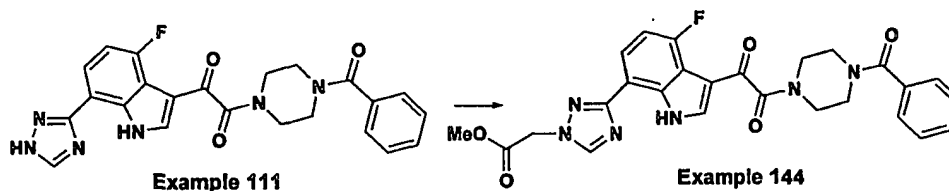
To a mixture of compound of Example 111 (100 mg, 0.224 mmol) in THF (2 ml) was added Cs$_2$CO$_3$ (80 mg, 0.246 mmol) and methyl bromoacetate (25
20   µl, 0.23 mmol). The reaction mixture was stirred at room temperature for 16 hours, and was then added additional portions of Cs$_2$CO$_3$ (200 mg, 0.614 mmol) and ethyl bromoacetate (0.1 ml, 0.90 mmol). The reaction mixture was stirred for a further 16 more hours, and added MeOH (4 ml), followed by filtration. The filtrate was purified by preparative reverse phase HPLC using
25   the method: Start %B = 20, Final %B = 80, Gradient time = 12 min, Flow Rate = 40 ml/min, Column : Xterra MS C-18 5µm 30 x 100 mm, Fraction Collection: 8.71 – 9.16 min. The position of the methyl acetate group at triazole N^1 was supported by H-C HMBC and H-H NOESY. ^{1}H NMR: (DMSO-d_6) δ 12.12 (s, 1H), 8.80 (s, 1H), 8.15 (d, J = 3.3, 1H), 7.98 (app dd, J
30   = 8.2, 4.3, 1H), 7.44 (b s, 5H), 7.16 (app t, J = 9.2, 1H), 5.36 (s, 2H), 3.80 – 3.30 (b m, 8H), 3.75 (s, overlapping with b m, 3H); LC/MS: (ES+) m/z (M+H)$^+$ = 519, HPLC R$_t$ = 1.283.

187

EXAMPLE 145

5   Compound of example 145 was prepared in the same manner as compound
of example 143. Purification was performed by reverse phase preparative
HPLC using the method: Start %B = 10, Final %B = 100, Gradient time = 15
min, Flow Rate = 40 ml/min, Column : Xterra MS C-18 5μm 30 x 100mm,
Fraction Collection: 8.70 – 9.15 min. ^{1}H NMR (CD$_3$OD) δ 8.52 (s, 1H), 8.12
10   (s, 1H), 7.95 (app, dd, J = 7.8, 4.4, 1H), 7.36 (b s, 5H), 7.01 (app, t, J = 8.9,
1H), 4.93 (s, 2H), 3.85 – 3.34 (b m, 8H), 2.77 (s, 3H); LC/MS (ES+) m/z
(M+H)$^+$ = 518, HPLC R$_t$ = 1.207.

Example 27   III

Example 146   Example 147

15

EXAMPLE 146

To the solution of compound of example 27 (crude, ca. 0.549 mmol) in
20   MeOH (3 ml) in a reusable sealed tube was added methyl propiolate (0.3 ml,
3.37 mmol) and triethylamine (0.2 ml). The tube was tightly sealed and the
reaction mixture was heated at 75°C for 2 hours. After cooled to room
temperature, the crude material was purified by preparative TLC (4:1
EtOAc/Hexane, 2 x 500 μm x 20 cm x 20 cm plates) to give intermediate III
25   as an off-white solid, which was directly used in the following reaction without

further purification. A mixture of intermediate III (47 mg, 0.09 mmol) and
phenyl ether (210 mg, 1.23 mmol) was heated to maintain gentle reflux for 10
minutes. The resulting black residue was added MeOH (4 ml) and filtered.
The filtrate was purified by reverse phase HPLC using the method: Start %B
5   = 30, Final %B = 100, Gradient time = 16 min, Flow Rate = 40 ml/min,
Column : YMC C18 S5 30 x 100 mm, Fraction Collection: 8.50– 9.00 min. ^{1}H
NMR: (CD$_3$OD) δ 8.25 (s, 1H), 7.96 (s, 1H), 7.75 (app dd, J = 8.3, 3.9, 1H),
7.46 (b s, 5H), 7.09 (app t, J = 9.6, 1H), 3.94 (s, overlapping with b m, 3H),
3.97 – 3.46 (b, m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 504, HPLC R$_t$ = 1.350.
10

EXAMPLE 147

To compound of Example 146 (15 mg, 0.030 mmol) was added an aqueous
solution of methylamine (0.5 ml, 40 wt. %). The resulting mixture was stirred
15 at room temperature for 16 hours. After removal of most of the solvent, the
resulting residue was added MeOH (2 ml) and purified by preparative reverse
phase HPLC using the method: Start %B = 20, Final %B = 85, Gradient time
= 10 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100 mm,
Fraction Collection: 7.16 – 7.67 min. ^{1}H NMR: (CD$_3$OD) δ 8.22 (s, 1H), 7.75
20 (s, overlapping with b m, 1H), 7.77 (b, m, 1H), 7.46 (b s, 5H), 7.09 (app t, J =
9.3, 1H), 3.97 – 3.45 (b m, 8H), 2.99 (s, 3H); LC/MS: (ES+) m/z (M+H)$^+$ =
503, HPLC R$_t$ = 1.223.
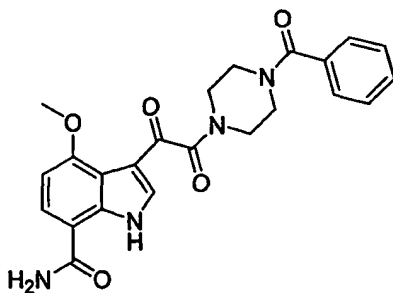
EXAMPLE 148
25

Compound of Example 148 was isolated as a minor product from the
following reaction to prepare hydroxyamidine: To an oven dried pressure
30 tube was added intermediate 46 (130 mg, 0.313 mmol), hydroxyamine
hydrochloride (65 .3 mg, 0939 mmol), EtOH (5ml) and triethylamine (142.5
mg, 0.196 ml, 1.41 mmol), and the resulting mixture stirred at 110 °C for 4 hr.

After cooling to rt., the mixture was purified reverse phase preparative HPLC to isolate the amide of Example 148 (10.5 mg, 8%) as a minor product, which was contaminated with 15% (based on ^{1}H-NMR) of its oxime derivative. ^{1}H NMR: (CD$_3$OD) δ 8.13 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.47 (b s, 5H), 6.83 (d, J = 8.3 Hz, 1H), 3.98 (s, 3H), 3.45-4.07 (m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 435, HPLC (YMC C18 S7 3 x 50 mm, Flow Rate 4 ml/min, Gradient Time 2 min) R$_t$ = 1.057.

EXAMPLE 149
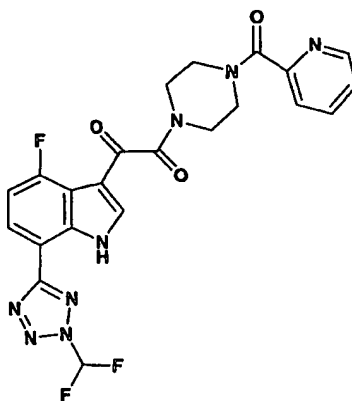
To a mixture of 18-Crown-6 (12 mg, 0.045 mmol), KF (3.7 mg, 0.064 mmol) and the tetrazole of Example 32 (26 mg, 0.058 mmol) in 2-methoxyethyl ether (0.5 ml) was added methyl 2-chloro-2,2-difluoroacetate (6.1 µl, 0.058 mmol). The reaction mixture was heated at 85°C for 5 hours, and was added more portions of KF (7 mg, 0.12 mmol) and methyl 2-chloro-2,2-difluoroacetate (6 µl, 0.057 mmol) and heated for 8 more hours. The reaction mixture was then added MeOH (2 ml), filtered and purified by reverse phase preparative HPLC using the method: Start %B = 40, Final %B = 75, Gradient time = 15 min, Flow Rate = 25 ml/min, Column : YMC C18 S5 20 x 100mm, Fraction Collection: 8.03 – 8.75 min ^{1}H NMR (CD$_3$OD) δ 8.64 and 8.56 (s, 1H), 8.42 – 8.20 (b m, 3H), 8.00 and 7.95 (t, J = 7.5, 1H), 7.67 (m, 1H), 7.55 and 7.49 (t, J = 5.9, 1H), 7.20 (dd, J = 20.2, 10.2, 1H), 3.94 – 3.58 (b m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 499, HPLC R$_t$ = 1.327.

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EXAMPLE 150
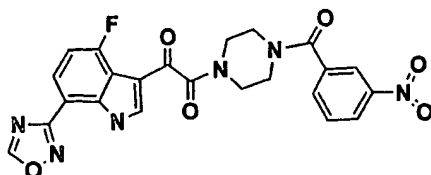
5   To a solution of intermediate 50 (ca. 0.644 mmol) in THF (6 ml) was added

N,N-diisopropylethylamine (0.5 ml) and intermediate 48 (210 mg, 0.77 mmol).

The reaction mixture was stirred at room temperature for 16 hours. After

concentrated *in vacuo*, the residue was added MeOH (6 ml) and purified by

reverse phase preparative HPLC using the method: Start %B = 20, Final %B

10   = 90, Gradient time = 12 min, Flow Rate = 40 ml/min, Column : YMC C18 S5

30 x 100mm, Fraction Collection: 8.44 – 8.89 min. **¹H NMR** (DMSO-d_6) δ

12.31 (s, 1H), 9.88 (s, 1H), 8.30 (b m, 2H), 8.11 (app d, J = 3.0, 1H), 8.09 (b

m, 1H), 7.89 (b m, 1H), 7.77 (b m, 1H), 7.27 (b m, 1H), 3.77 – 3.40 (b m,

overlapping with broad water peak, 8H); **LC/MS** (ES+) m/z (M+H)⁺ = 493,

15   HPLC R_t = 1.340.

EXAMPLE 151
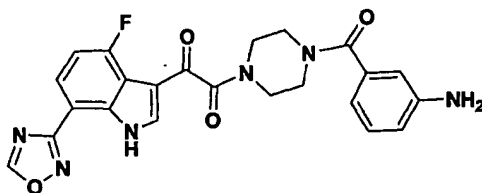
20 .

To compound of Example 150 (50 mg, 0.102 mmol) in MeOH (3 ml) was

added palladium on activated carbon (36 mg, 10%). The reaction mixture

was stirred at room temperature under a hydrogen atmosphere for 16 hours.

After passing through a short Celite®545 pad, the filtrate was purified by

25   reverse phase HPLC using the method: Start %B = 15, Final %B = 85,

Gradient time = 12 min, Flow Rate = 40 ml/min, Column : XTerra MS C-18

5μm 30 x 100mm, Fraction Collection: 6.65 – 7.10 min. **¹H NMR** (CD₃OD) δ

191

9.27 (s, 1H), 8.21 (s, 1H), 8.12 (b m, 1H), 7.35 (b m, 1H), 7.14 - 7.06 (b m, 4H), 3.87 – 3.51 (b m, 8H); **LC/MS** (ES+) m/z (M+H)$^+$ = 463, HPLC R$_t$ = 1.033
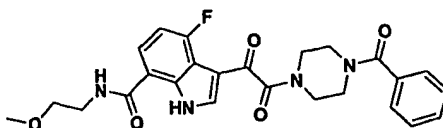
EXAMPLE 152

Compound of Example 152 was prepared in the same manner as compound of Example 64, except that THF was used as the solvent for coupling of the acid chloride of intermediate 23 to excess 2-methoxyethylamine in the absence of pyridine. The crude residue obtained after evaporation of the volatile was purified by preparative TLC (5% MeOH/CH$_2$Cl$_2$, 50 m x 20 cm x 20 cm plate). **^{1}H NMR:** (CD$_3$OD) δ 8.17 (s, 1H), 7.77 (dd, J = 8.1, 4.0, 1H), 7.46 (b m, 5H), 7.03 (app t, 1H), 4.00–3.45 (b m, 8H), 3.62–3.60 (m overlapped with b m, 4H), 3.39 (s, 3H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 481, HPLC R$_t$ = 1.253.
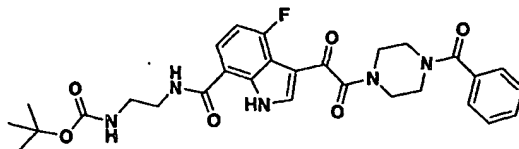
EXAMPLE 153

Compound of Example 153 was prepared in the same manner as compound of Example 152. **^{1}H NMR:** (CDCl$_3$) δ 11.40 (b s, 1H), 8.13 (d, J = 3.0, 1H), 7.86 (b s, 1H), 7.59 (dd, J = 8.0, 3.5, 1H), 7.43 (b m, 5H), 6.99 (app t, 1H), 5.04 (b s, 1H), 4.00–3.25 (b overlapping m, 12H), 1.44 (s, 9H); **LC/MS:** (ES+) m/z (M+H)$^+$ = 566, HPLC R$_t$ = 1.340.

EXAMPLE 154

192
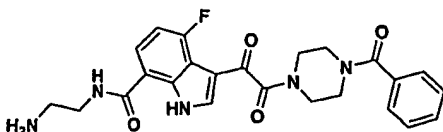
The hydrochloride salt of Example 154 was prepared by treating compound of Example 153 with an excess of a solution of HCl in dioxane (4 *M*). ^{1}H NMR: (300 MHz, CD$_3$OD) δ 8.21 (s, 1H), 7.84 (b dd, 1H), 7.48 (b m, 5H), 7.08 (b app t, 1H), 4.00–3.45 (b overlapping m, 12H); LC/MS: (ES+) m/z

5   (M+H)$^+$ = 466, HPLC R$_t$ = 0.920.

EXAMPLE 155

10
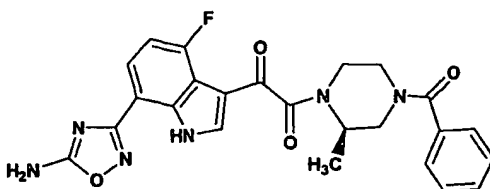
Compound of Example 155 was prepared in the same manner as compound of Example 83. Purification was performed by preparative reverse phase HPLC using the method: Start %B = 20, Final %B = 100, Gradient time = 12 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100mm, Fraction

15   Collection: 8.04 – 8.49 min. ^{1}H NMR (CDCl$_3$) δ 10.58 (s, 1H), 8.14 (s,1H), 7.87 (b m, 1H), 7.43 (b m, 5H), 7.08 (app t, *J* = 9.2, 1H), 5.92(s, 2H), 5.05 – 3.07 (b m, 7H), 1.39 – 1.15 (b m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 477, HPLC R$_t$ = 1.356.

20   Compound of Examples 156 to 162 were prepared analogously to compound of Example 82.

EXAMPLE 156
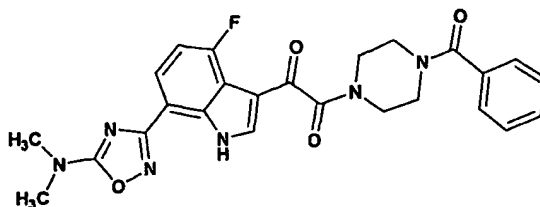
25

Purification was performed by preparative reverse phase HPLC using the method: Start %B = 20, Final %B = 100, Gradient time = 12 min, Flow Rate = 25 ml/min, Column : YMC C18 S5 20 x 100mm, Fraction Collection: 10.52 –

30   11.24 min. ^{1}H NMR (CDCl$_3$) δ 10.72(s, 1H), 8.16 (s,1H), 7.99 (app dd, *J* =

8.2, 4.3, 1H), 7.43 (b s, 5H), 7.07 (app t, J = 9.3, 1H), 3.85 – 3.40 (b m, 8H), 3.26 (s, 6H); **LC/MS** (ES+) m/z (M+H)$^+$= 491, HPLC R$_t$ = 1.503.
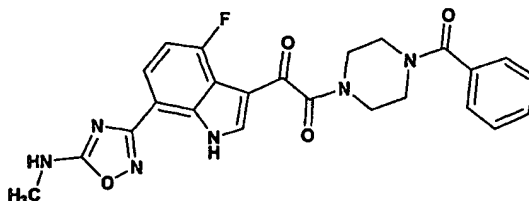
EXAMPLE 157

5

Purification was performed by preparative reverse phase HPLC using the method: Start %B = 10, Final %B = 100, Gradient time = 12 min, Flow Rate =

10   25 ml/min, Column : YMC C18 S5 20 x 100mm, Fraction Collection: 9.47 – 9.82 min. **^{1}H NMR** (CDCl$_3$) δ 10.66(s, 1H), 8.17 (d, J = 2.7, 1H), 7.97 (app dd, J = 8.2, 4.2, 1H), 7.43 (b s, 5H), 7.09 (app t, J = 9.3, 1H), 5.59 (b s, 1H), 3.85 – 3.50 (b m, 8H), 3.20 (d, J = 5.0, 3H); **LC/MS** (ES+) m/z (M+H)$^+$= 477, HPLC R$_t$ = 1.360.

15

EXAMPLE 158
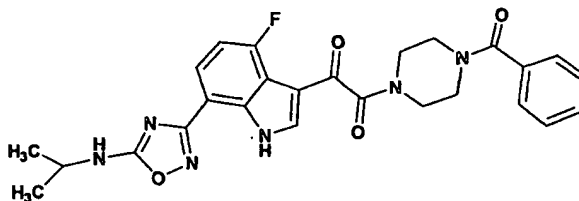
20   Purification was performed by preparative reverse phase HPLC using the similar method as that of compound of Example 157. ^{1}H NMR (300 MHz, CDCl$_3$) δ 10.70 (s, 1H), 8.18 (s,1H), 8.01 (app dd, J = 8.3, 4.6, 1H), 7.45 (b s, 5H), 7.09 (app t J = 9.4, 1H), 5.24 (d, J = 7.4, 1H), 4.09 (app, dd, J = 13.3, 6.7, 1H), 3.81 – 3.51 (b m, 8H), 1.39 (d, J = 6.5, 6H); LC/MS (ES+) m/z
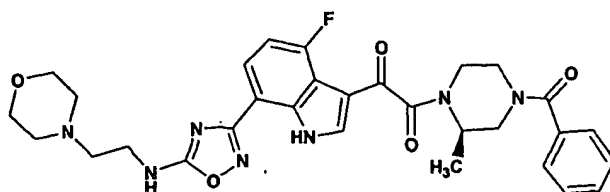
25   (M+H)$^+$= 505, HPLC R$_t$ = 1.587.

194

EXAMPLE 159

5   Purification was performed by preparative reverse phase HPLC using the method: Start %B = 20, Final %B = 90, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100mm, Fraction Collection: 8.71 – 9.17 min. ^{1}H NMR (CDCl$_3$) δ 10.81 (d, J = 11.5, 1H), 8.10 (d, J = 6.2,1H), 7.77 (b m, 1H), 7.42 (b s, 5H), 6.95 (app t, J = 8.3, 1H), 5.00 – 2.47 (broad

10   overlapping m, 20H), 1.40 – 1.22 (b m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 590, HPLC R$_t$ = 1.226.

EXAMPLE 160
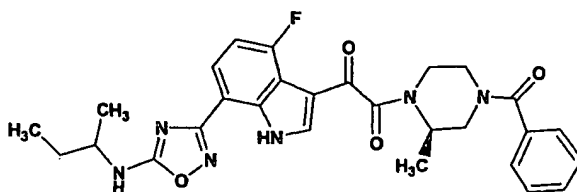
15

Purification was performed by preparative reverse phase HPLC using a similar method as that of compound of Example 159. ^{1}H NMR (CDCl$_3$) δ 10.69 (s, 1H), 8.12 (app dd, J = 4.7, 3.3, 1H), 7.98 (app dd, J = 7.5, 4.5, 1H),

20   7.43 (b s, 5H), 7.07 (app t, J = 10.5, 1H), 5.12 (d, J = 9.0, 1H), 3.88 (m, overlapping with b m, 1H), 5.00 – 2.96 (b m, 7H), 1.69 (m, 2H), 1.36 (overlapping b m, 6H), 1.00 (m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 533, HPLC R$_t$ = 1.689.

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EXAMPLE 161
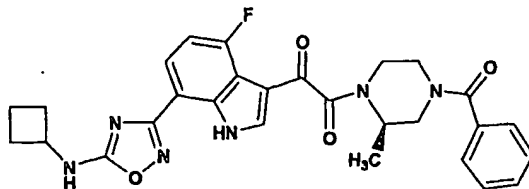
5   Purification was performed by preparative reverse phase HPLC using a similar method as that of compound of Example 159. ^{1}H NMR (CDCl$_3$) δ 10.69 (s, 1H), 8.12 (app dd, J = 5.2, 3.3,1H), 7.96 (app dd, J = 8.0, 4.0,1H), 7.42 (b s, 5H), 7.05 (app t, J = 8.5, 1H), 5.55 (dd, J = 7.3, 3.8, 1H), 4.35 (app, dd, overlapping with b m, J = 16.2, 7.8,1H), 5.10 – 2.88 (b m, 7H), 2.34 (m,

10   2H), 2.07 (m, 2H), 1.82 (m, 2H), 1.39 -1.20 (b m, 3H); **LC/MS** (ES+) m/z (M+H)$^+$ = 531, HPLC R$_t$ = 1.676.

EXAMPLE 162
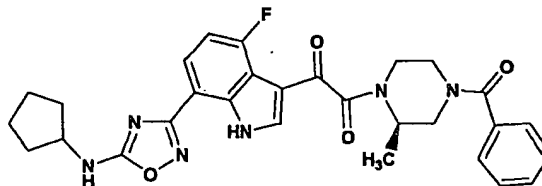
15

Purification was performed by preparative reverse phase HPLC using a similar method as that of compound of Example 159. ^{1}H NMR (CODCl$_3$) δ 10.71 (s, 1H), 8.12 (b m,1H), 7.97 (app dd, J = 7.8, 4.3, 1H), 7.42 (b s, 5H),

20   7.07 (app t, J = 8.5, 1H), 5.31 (d, J = 6.5, 1H), 4.81 – 2.88 (broad overlapping m, 8H), 2.18 – 1.26 (broad overlapping m, 11H); **LC/MS** (ES+) m/z (M+H)$^+$ = 545, HPLC R$_t$ = 1.729.

Compound of Examples 163 to 165 were prepared analogously to compound

25   of Example 76.

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EXAMPLE 163
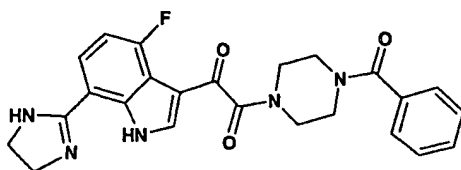
5   Purification was performed by preparative reverse phase HPLC using the
method: Start %B = 0, Final %B = 75, Gradient time = 15 min, Flow Rate =
25 ml/min, Column : YMC C18 S5 20 x 100mm, Fraction Collection: 8.79 –
9.18 min. ^{1}H NMR (CD$_3$OD) δ 8.31 (s,1H), 7.70 (app dd, J = 8.2, 4.1, 1H),
7.47 (b s, 5H), 7.20 (app t, J = 9.4, 1H), 4.17 (s, 4H), 3.79 – 3.34 (b m, 8H);

10   LC/MS (ES+) m/z (M+H)$^+$ = 448, HPLC R$_t$ = 0.983.

EXAMPLE 164
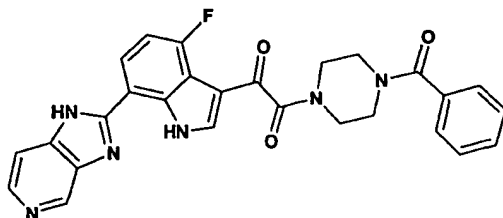
15

Purification was performed by preparative reverse phase HPLC using the
method: Start %B = 20, Final %B = 75, Gradient time = 15 min, Flow Rate =
25 ml/min, Column : YMC C18 S5 20 x 100mm, Fraction Collection: 8.79 –
9.42 min. ^{1}H NMR (CD$_3$OD) δ 9.29 (b s,1H), 8.57 (d, J = 6.5, 1H), 8.34 (s,

20   1H), 8.16 (b m, 2H), 7.47 (b s, 5H), 7.27 (app t, J = 9.3, 1H), 3.98 – 3.44 (b
m, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 497, HPLC R$_t$ = 1.200.

EXAMPLE 165
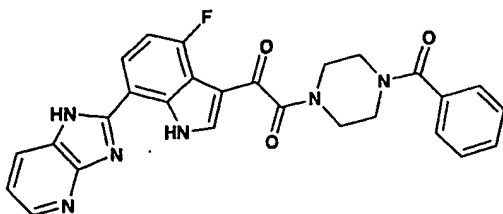
25

Purification was performed by preparative HPLC using the method: Start %B = 20, Final %B = 80, Gradient time = 14 min, Flow Rate = 25 ml/min, Column : YMC C18 S5 20 x 100mm, Fraction Collection: 11.89 – 12.34 min. ^{1}H NMR (CD$_3$OD) δ 8.51 (d, J = 4.9,1H), 8.34 (b s, 2H), 8.08 (b m, 1H), 7.55 (app, dd, J = 13.5, 8.3, 1H), 7.47 (b s, 5H), 7.22(app, t, J = 8.5,1H), 3.81 – 3.44 (b m, 8H); **LC/MS** (ES+) m/z (M+H)$^+$ = 497, HPLC R$_t$ = 1.227.

EXAMPLE 166
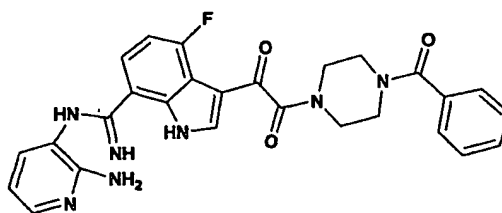
Compound of Example 166 was isolated as a side product in the preparation of compound of Example 165. Purification was performed by preparative reverse phase HPLC using the method: Start %B = 20, Final %B = 80, Gradient time = 14 min, Flow Rate = 25 ml/min, Column : YMC C18 S5 20 x 100mm, Fraction Collection: 7.88 – 8.16 min. ^{1}H NMR (CD$_3$OD) δ 8.20 (s,1H), 7.89 (b m, 1H), 7.73 (b m, 2H), 7.47 (b s, 5H), 7.15 (b m, 1H), 6.95 (b m, 1H), 3.89 – 3.44 (b m, 8H); **LC/MS** (ES+) m/z (M+H)$^+$ = 514, HPLC R$_t$ = 0.913.

Methods of the preparation of compounds of Examples 167 to 193 can be found in the analogous Examples described above.
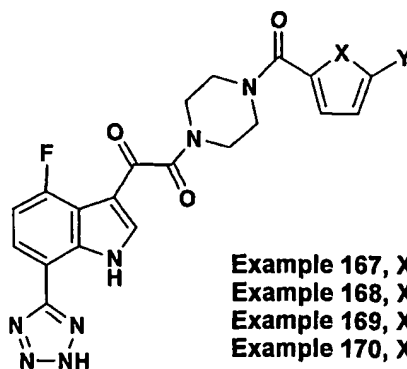
Example 167, X = O, Y = H
Example 168, X = O, Y = Cl
Example 169, X = O, Y = Br
Example 170, X = S, Y = H

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EXAMPLE 167

Separation method: Start %B = 10, Final %B = 75, Gradient time = 12 min, Flow Rate = 30 ml/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 6.93 – 8.06 min. ^{1}H NMR: (DMSO-d_6) δ 12.52 (s, 1H), 8.41 (app d, J = 3.3, 1H), 7.99 (app dd, J = 8.3, 4.2, 1H), 7.86 (app s, 1H), 7.33 (app dd, J = 10.3, 8.4, 1H), 7.04 (app d, J = 3.2, 1H), 6.64 (app s, 1H), 3.81 – 3.47 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 438, (2M+H)$^+$ = 875, HPLC R_t = 1.123.

EXAMPLE 168

Separation method: Start %B = 20, Final %B = 85, Gradient time = 12 min, Flow Rate = 30 ml/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 7.01 – 7.62 min. ^{1}H NMR: (DMSO) δ 12.53 (s, 1H), 8.20 (s, 1H), 7.98 (app dd, J = 8.1, 3.9, 1H), 7.32 (app dd, J = 10.3, 8.4, 1H), 7.13 (d, J =3.4, 1H), 6.70 (d, J = 3.4, 1H), 3.73 – 3.47 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 472, HPLC R_t = 1.267 .

EXAMPLE 169

Separation method: Start %B = 0, Final %B = 100, Gradient time = 10 min, Flow Rate = 30 ml/min, Column YMC C18 S5 20 x 50mm, Fraction Collection: 6.90 – 7.15 min. ^{1}H NMR: (DMSO) δ 12.53 (s, 1H), 8.20 (s, 1H), 7.98 (app dd, J = 8.0, 4.0, 1H), 7.32 (app dd, J = 10.2, 8.2, 1H), 7.08 (d, J = 3.5, 1H), 6.78 (d, J = 3.5, 1H), 3.79 – 3.42 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 517, HPLC R_t = 1.293.

EXAMPLE 170

Separation method: Start %B = 20, Final %B = 75, Gradient time = 14 min, Flow Rate = 30 ml/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 6.85 – 8.07 min. ^{1}H NMR: (DMSO) δ 12.53 (s, 1H), 8.20 (app d, J = 3.2, 1H), 7.98 (app dd, J = 8.4, 4.2, 1H), 7.79 (app dd, J = 5.0, 0.90, 1H), 7.46 (d, J = 3.2, 1H), 7.32 (app dd, J = 10.3, 8.4, 1H), 7.14 (app t, J = 4.2, 1H), 3.80 – 3.66 (b m, 8H); LC/MS: (ES+) m/z (M+H)$^+$ = 454, HPLC R_t = 1.170.

199
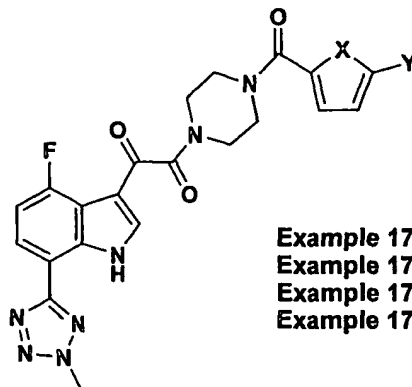
Example 171, X = O, Y = H
Example 172, X = O, Y = Cl
Example 173, X = O, Y = Br
Example 174, X = S, Y = H

EXAMPLE 171

Separation method: Start %B = 30, Final %B = 100, Gradient time = 15 min, Flow Rate = 35 ml/min, Column: YMC C18 S5 30 x 100mm, Fraction Collection: 8.30 – 8.82 min. ^{1}H NMR: (CDCl$_3$) δ 11.03 (s, 1H), 8.24 (app d, J = 3.1, 1H), 8.09 (app dd, J = 8.4, 4.4, 1H), 7.53 (app s, 1H), 7.13 (m, 2H), 6.53 (app dd, J = 3.3, 1.6, 1H), 4.49 (s, 3H), 4.00 – 3.87 (b m, 6H), 3.68 (m, 2H); LC/MS: (ES+) m/z (M+H)$^+$ = 452, HPLC R$_t$ = 1.240.

EXAMPLE 172

Separation method: Start %B = 20, Final %B = 100, Gradient time = 12 min, Flow Rate = 30 ml/min, Column: YMC C18 S5 30 x 100mm, Fraction Collection: 7.17 – 7.34 min. ^{1}H NMR: (TFA solvate, CDCl$_3$) δ 11.01 (s, 1H), 8.24 (app d, J = 3.1, 1H), 8.09 (app dd, J = 8.3, 4.4, 1H), 7.13 (app dd, J = 10.4, 8.3, 1H), 7.08 (d, J = 3.6, 1H), 6.31 (d, J = 3.6, 1H), 4.49 (s, 3H), 3.95 – 3.86 (b m, 6H), 3.66 (m, 2H); LC/MS: (ES+) m/z (M+H)$^+$ = 486, HPLC R$_t$ = 1.383.

EXAMPLE 173

Separation method: Start %B = 20, Final %B = 100, Gradient time = 12 min, Flow Rate = 35 ml/min, Column: YMC C18 S5 30 x 100mm, Fraction Collection: 9.76 – 10.24 min. ^{1}H NMR : (CDCl$_3$) δ 11.01 (s, 1H), 8.23 (app d, J = 3.1, 1H), 8.10 (app dd, J = 8.4, 4.4, 1H), 7.13 (app dd, J = 10.4, 8.3, 1H), 7.05 (d, J = 3.5, 1H), 6.45 (d, J = 3.5, 1H), 4.49 (s, 3H), 3.88 – 3.86 (b m, 6H), 3.66 (m, 2H); LC/MS: (ES+) m/z (M+H)$^+$ = 531, HPLC R$_t$ = 1.397.

EXAMPLE 174

Separation method: Start %B = 30, Final %B = 100, Gradient time = 12 min, Flow Rate = 35 ml/min, Column: YMC C18 S5 30 x 100mm, Fraction Collection: 7.92 – 8.45 min. ^{1}H NMR: (CDCl$_3$) δ 11.02 (s, 1H), 8.23 (app d, J = 3.1, 1H), 8.10 (app dd, J = 8.4, 4.4, 1H), 7.50 (app dd, J = 5.0, 1.0, 1H), 7.34 (app dd, J = 3.6, 0.95, 1H), 7.12 (app dd, J = 10.4, 8.4, 1H), 7.08 (app dd, J = 5.0, 3.7, 1H), 4.49 (s, 3H), 3.93 (m, 2H), 3.85 (m, 4H), 3.64 (m, 2H); LC/MS: (ES+) m/z (M+H)$^+$ = 468, HPLC R$_t$ = 1.287 .
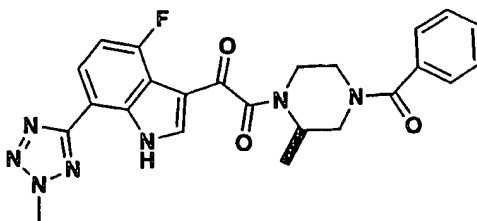
EXAMPLE 175

Separation method Start %B = 30, Final %B = 100, Gradient time = 8 min, Flow Rate = 25 ml/min, Column: YMC C18 S5 20 x 50mm, Fraction Collection: 4.71 – 5.41 min. ^{1}H NMR: (CD$_3$OD) δ 8.25 and 8.21 (s, 1H), 8.13 (b s, 1H), 7.46 (b m, 5H), 7.15 (b s, 1H), 4.49 (2, 3H), 3.0 – 4.80 (very b m, 7H), 1.15 – 1.45 (b m, 3H); LC/MS: (ES+) m/z (M+H)$^+$ = 476, HPLC R$_t$ = 1.353.
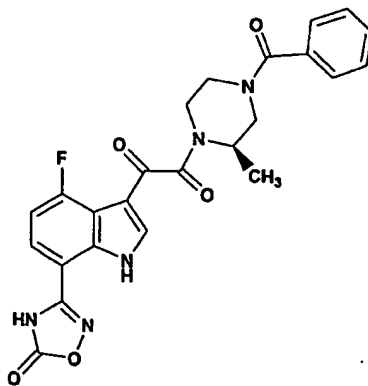
EXAMPLE 176

Purification was performed by preparative HPLC using the method: Start %B = 30, Final %B = 100, Gradient time = 14 min, Flow Rate = 25 ml/min,. Column : YMC C18 S5 20 x 100mm, Fraction Collection: 6.73 – 8.20 min. ^{1}H NMR (mixture of conformers, CD$_3$OD) δ 8.26 and 8.17 (s, 1H), 7.66 (b m, 1H), 7.46 (b s, 5H), 7.16 (b m, 1H), 4.73 – 2.99 (b m, 7H), 1.46 – 1.24 (b m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 478, HPLC R$_t$ = 1.237.

EXAMPLE 177
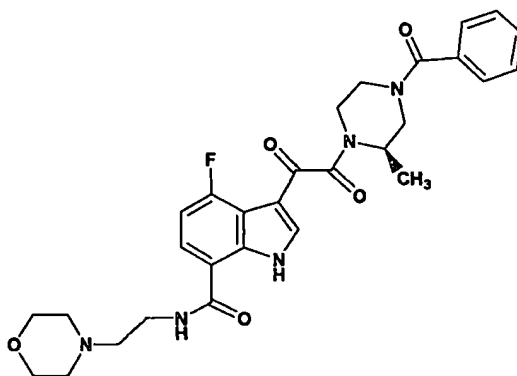
Purification was performed by preparative HPLC using the method: Start %B = 10, Final %B = 80, Gradient time = 12 min, Flow Rate = 25 ml/min, Column : YMC C18 S5 20 x 100mm, Fraction Collection: 7.17 – 7.90 min. ^{1}H NMR (mixture of conformers, CD$_3$OD) δ 8.19 and 8.15 (s, 1H), 7.80 (b m, 1H), 7.48 (b s, 5H), 7.07 (app t, J = 8.1, 1H), 3.84 (t, overlapping with b m, J = 5.6, 2H), 3.45 (t, overlapping with b m, J = 5.6, 2H), 4.84 – 3.09 (b overlapping m, 15H), 1.37 – 1.25 (b m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 550, HPLC R$_t$ = 1.040.
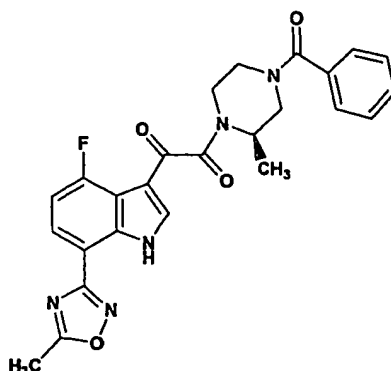
202

EXAMPLE 178

Purification was performed by preparative HPLC using the method: Start %B
= 20, Final %B = 90, Gradient time = 15 min, Flow Rate = 25 ml/min, Column
: YMC C18 S5 20 x 100mm, Fraction Collection: 11.55 – 12.27 min. ^{1}H NMR
(mixture of conformers, CD$_3$OD) δ 8.22 and 8.18 (s, 1H), 8.07 (b m, 1H), 7.46
(b s, 5H), 7.15 (b m, 1H), 4.82 – 3.10 (b m, 7H), 2.72 (s, 3H), 1.39 – 1.25 (b
m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 476, HPLC R$_t$ = 1.403.
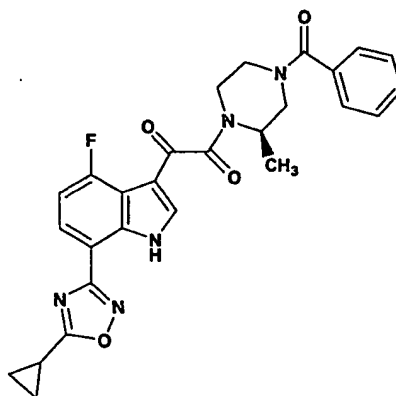
EXAMPLE 179

Purification was performed by preparative HPLC using the method: Start %B
= 30, Final %B = 100, Gradient time = 14 min, Flow Rate = 25 ml/min,
Column : YMC C18 S5 20 x 100mm, Fraction Collection: 11.05 – 11.77 min.
^{1}H NMR (mixture of conformers, CD$_3$OD) δ 8.21 and 8.17 (s, 1H), 8.04 (b m,
1H), 7.46 (b s, 5H), 7.13 (b m, 1H), 4.80 – 3.11 (b m, 7H), 2.40 (m, 1H), 1.38
– 1.25 (overlapping b m, 7H); LC/MS (ES+) m/z (M+H)$^+$ = 502, HPLC R$_t$ =
1.520.

203
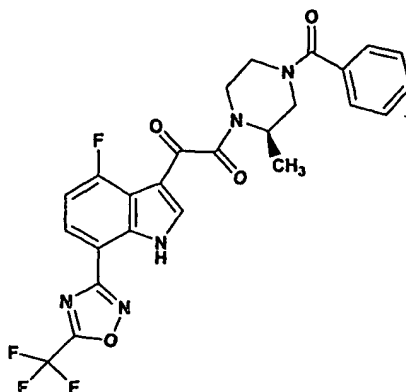
EXAMPLE 180

5 Purification was performed by preparative HPLC using the method: Start %B = 30, Final %B = 100, Gradient time = 14 min, Flow Rate = 25 ml/min, Column : YMC C18 S5 20 x 100mm, Fraction Collection: 12.05 – 12.77 min. ^{1}H NMR (CDCl$_3$) δ 10.36 (s, 1H), 8.22 (d, J = 4.2, 1H), 8.17 (app, dd, J = 7.8, 4.1, 1H), 7.43 (b s, 5H), 7.17 (app t, J = 9.3, 1H), 4.90 – 3.00 (b m, 7H), 1.40

10 – 1.29 (b m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 530, HPLC R$_t$ = 1.613.
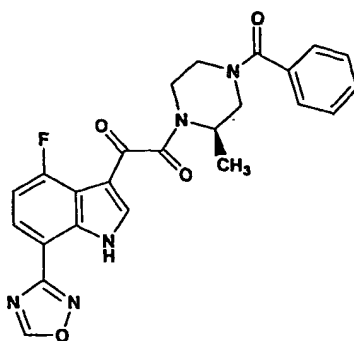
EXAMPLE 181

15

Purification was performed by preparative HPLC using the method: Start %B = 30, Final %B = 100, Gradient time = 15 min, Flow Rate = 30 ml/min, Column : YMC C18 S5 20 x 100mm, Fraction Collection: 6.32 – 6.93 min. ^{1}H NMR (CD$_3$OD) δ 9.41(s, 1H), 8.23 and 8.20 (s, 1H), 8.15 (b m, 1H), 7.46 (b

20 s, 5H), 7.18 (b m, 1H), 4.79 – 3.07 (b m, 7H), 1.39 – 1.18 (b m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 462, HPLC R$_t$ = 1.350.

204
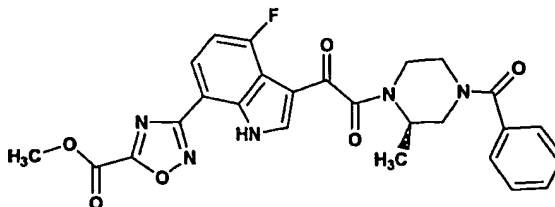
EXAMPLE 182

5   Purification was performed by preparative HPLC using the method: Start %B
       = 20, Final %B = 80, Gradient time = 15 min, Flow Rate = 40 ml/min, Column
       : YMC C18 S5 30 x 100mm, Fraction Collection: 13.60 – 14.04 min. ^{1}H NMR
       (CDCl$_3$) δ 10.56 (s, 1H), 8.21 (overlapping m, 2H), 7.26 (b m, 5H), 7.15 (app
       t, J = 9.3, 1H), 4.16(s, overlapping with b m, 3H), 5.10 – 3.00 (b m, 7H), 1.50
10   – 1.20 (b m, 3H); LC/MS (ES+) m/z (M+H)$^+$ = 520, HPLC R$_t$ = 1.500.
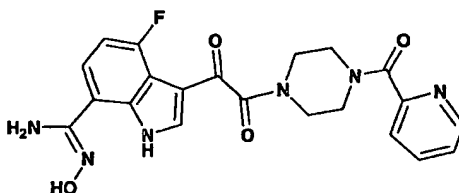
EXAMPLE 183

15

       Purification was performed by preparative HPLC using the method: Start %B
       = 0, Final %B = 75, Gradient time = 10 min, Flow Rate = 40 ml/min, Column :
       YMC C18 S5 30 x 100mm, Fraction Collection: 4.34 – 5.06 min. ^{1}H NMR
       (DMSO-d$_6$) δ 13.97 (d, J = 15.0, 1H), 10.47 (b, s, 2H), 9.17 (b s, 1H), 8.64
20   and 8.54 (d, J = 4.5,1H), 8.39 (t, J = 3.3, 1H), 7.96 (m, 1H), 7.65 - 7.46 (b m,
       3H), 7.22 (b m, 1H), 3.83 (app d, J = 5.5, 1H), 3.75 (app d, J = 5.3, 1H), 3.66
       (app d, J = 3.4, 2H), 3.61 (app t, J = 2.6, 1H), 3.48 (app t, J = 4.8, 1H), 3.44
       (app t, J = 2.8, 1H), 3.90 (app d, J = 5.2, 1H); LC/MS (ES+) m/z (M+H)$^+$ =
       439, HPLC R$_t$ = 0.740.
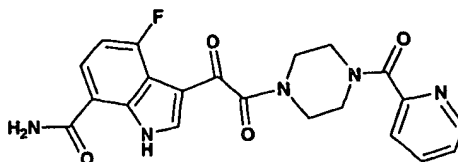
EXAMPLE 184

5   Purification was performed by preparative HPLC using the method: Start %B
= 0, Final %B = 75, Gradient time = 10 min, Flow Rate = 40 ml/min. Column :
YMC C18 S5 30 x 100mm, Fraction Collection: 6.43 − 7.15 min. ^{1}H NMR
(DMSO-d_6) δ 12.39 (d, J = 12.0, 1H), 8.63 and 8.54 (d, J = 4.5,1H), 8.24 (b s,
1H), 8.08 (d, J = 2.9, 1H), 7.99 − 7.87(b m, 2H), 7.63 (m, 2H), 7.52 and 7.46
10 (app dd, J = 7.0, 5.2, 1H), 7.10 (b m, 1H), 3.79 (app t, J = 2.8, 1H), 3.74 (app
d, J = 5.5, 1H), 3.65 (app d, J = 2.7, 2H), 3.57 (app d, J = 5.4, 1H), 3.48 (app
d, J = 4.9, 1H), 3.42 (app d, J = 5.7, 1H), 3.39 (app d, J = 5.4, 1H); **LC/MS**
(ES+) m/z (M+H)$^+$ = 424, HPLC R_t = 0.903.

15   **EXAMPLE 185A**
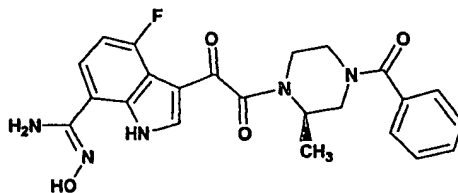
Purification was performed by preparative HPLC using the method: Start %B
20 = 10, Final %B = 80, Gradient time = 12 min, Flow Rate = 25 ml/min, Column
: YMC C18 S5 20 x 100mm, Fraction Collection: 5.82 − 7.28 min. ^{1}H NMR
(CD$_3$OD) δ 8.26 and 8.21 (s, 1H), 7.56 (b m, 1H), 7.46 (b s, 5H), 7.15 (b m,
1H), 4.83 − 3.11 (b m, 7H), 1.37 − 1.16 (b m, 3H); **LC/MS** (ES+) m/z (M+H)$^+$ =
452, HPLC R_t = 0.937.

25

                                      EXAMPLE 185B

Purification was performed by preparative HPLC using the method: Start %B = 0, Final %B = 100, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100mm, Fraction Collection: 5.80 – 5.06 min. ¹H NMR (DMSO-d_6) δ 12.71 (b s, 1H), 11.10 (b, s, 1H), 8.64 and 8.54 (app dd, J = 9.6, 4.7,1H), 8.36 – 8.26 (b m,1H), 7.99 – 7.95 (b m, 1H), 7.67 – 7.46 (b m, 3H), 7.23 - 7.17 (b m, 1H), 6.10 (b s, 2H), 4.81 – 2.91 (b m, 7H), 1.29 – 1.11 (b m, 3H); LC/MS (ES+) m/z (M+H)⁺ = 453, HPLC R_t = 0.793.

EXAMPLE 186A
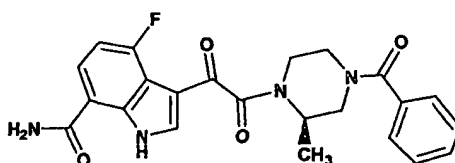
Purification was performed by preparative HPLC using the method: Start %B = 10, Final %B = 80, Gradient time = 12 min, Flow Rate = 25 ml/min, Column : YMC C18 S5 20 x 100mm, Fraction Collection: 8.10 – 8.83 min. ¹H NMR (CD₃OD) δ 8.18 and 8.14 (s, 1H), 7.83 (b m, 1H), 7.46 (b s, 5H), 7.04 (b m, 1H), 4.83 – 3.11 (b m, 7H), 1.38 – 1.25 (b m, 3H); LC/MS (ES+) m/z (M+H)⁺ = 437, HPLC R_t = 1.113.

EXAMPLE 186B
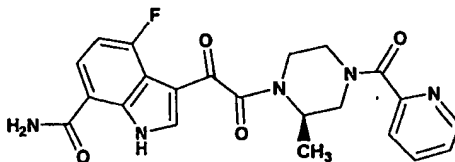
Purification was performed by preparative HPLC using the method: Start %B = 0, Final %B = 100, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100mm, Fraction Collection: 7.94 – 8.39 min. ¹H NMR (DMSO-d_6) δ 12.37 (b m, 1H), 8.64 and 88.54 (app dd, J = 10.6, 4.7, 1H), 8.23 (app d, J = 6.4,1H), 8.08 – 7.88 (b m, 3H), 7.66 – 7.46 (b m, 3H), 7.15 - 7.08 (b m, 1H),4.98 – 2.89 (b m, 7H), 1.27 – 1.10 (b m, 3H); LC/MS (ES+) m/z (M+H)⁺ = 438, HPLC R_t = 0.960.

EXAMPLE 187
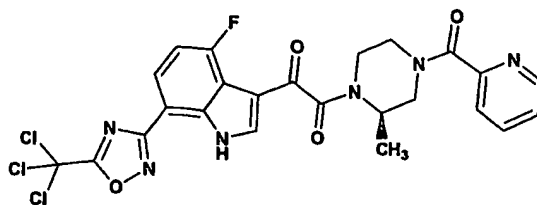
5   Purification was performed by preparative HPLC using the method: Start %B
     = 30, Final %B = 100, Gradient time = 16 min, Flow Rate = 30 ml/min,
     Column : YMC C18 S5 30 x 100mm, Fraction Collection: 14.81 – 15.37 min.
     ^{1}H NMR (CDCl$_3$) δ 10.43 (d, J = 8.0, 1H), 8.71 – 8.58 (b m, 1H), 8.21 – 8.16
     (b m,2H), 7.95 – 7.86 (b m, 1H), 7.73 (b s, 1H), 7.49 - 7.43 (b m, 1H), 7.18 –
10   7.12 (b m, 1H), 5.05 – 3.08 (b m, 7H), 1.45 and 1.29 (b m, 3H); LC/MS (ES+)
     m/z (M+H)$^+$ = 580, HPLC R$_t$ = 1.773.
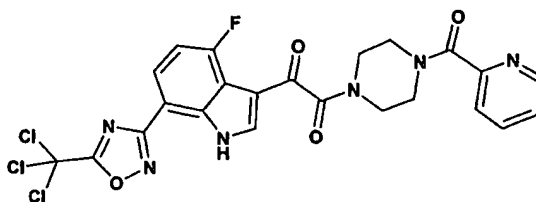
EXAMPLE 188

15

     Purification was performed by preparative HPLC using the method: Start %B
     = 10, Final %B = 100, Gradient time = 12 min, Flow Rate = 40 ml/min,
     Column : YMC C18 S5 30 x 100mm, Fraction Collection: 12.77 – 13.37 min.
20   ^{1}H NMR (CDCl$_3$) δ 10.47 (b s, 1H), 8.77 and 8.69 (b s, 1H), 8.25 (app d, J =
     2.8,1H), 8.18 (b s, 1H), 8.04(b m, 1H), 7.74 (b s, 1H), 7.62 - 7.57 (b m, 1H),
     7.15 (app dd, J = 17.9, 8.6, 1H), 3.98 – 3.59 (b m, 8H); LC/MS (ES+) m/z
     (M+H)$^+$ = 566, HPLC R$_t$ = 1.750.

25   ## EXAMPLE 189

208
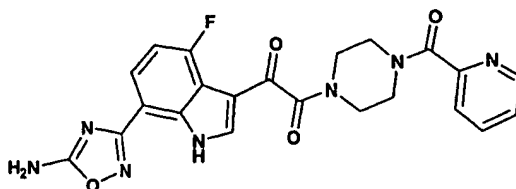
Purification was performed by preparative HPLC using a similar method as that of compound of Example 190. ^{1}H NMR (DMSO-d_6) δ 12.00 (d, J = 12.0,1H), 8.64 and 8.54 (app d, J = 5.0, 1H), 8.13 (b s, 3H), 7.98 – 7.85 (b m, 2H), 7.62 (app dd, J = 14.0, 8.0, 1H), 7.52 and 7.46 (b m, 1H), 7.19 (b m, 1H), 3.80 (app d, J = 6.0, 1H), 3.75 (app d, J = 6.0, 1H), 3.65 (app d, J = 3.0, 2H), 3.5 8 (app d, J = 5.5, 1H), 3.49 (app d, J = 5.0, 1H), 3.42 (app d, J = 7.5, 2H); **LC/MS** (ES+) m/z (M+H)$^+$ = 464, HPLC R$_t$ = 1.123.

EXAMPLE 190

Purification was performed by preparative HPLC using the method: Start %B = 20, Final %B = 100, Gradient time = 15 min, Flow Rate = 30 ml/min, Column : YMC C18 S5 30 x 100mm, Fraction Collection: 8.96 – 8.98 min. ^{1}H NMR (CD$_3$OD) δ 8.65 – 8.52 (b m, 1H), 8.24 (m, 1H), 7.99 – 7.91 (b m, 2H), 7.67 (m, 1H), 7.56 – 7.47 (b m, 1H), 7.10 (b m, 1H), 4.69 – 3.06 (b m, 7H), 1.40 and 1.26 (b m, 3H); **LC/MS** (ES+) m/z (M+H)$^+$ = 478, HPLC R$_t$ = 1.173.

EXAMPLE 191
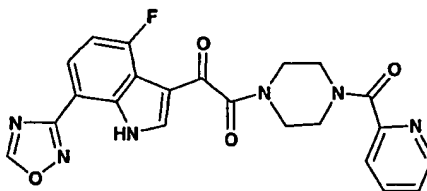
Purification was performed by preparative HPLC using the method: Start %B = 10, Final %B = 90, Gradient time = 15 min, Flow Rate = 40 ml/min, Column : YMC C18 S5 30 x 100mm, Fraction Collection: 9.79 – 10.25 min. ^{1}H NMR (CDCl$_3$) δ 10.66 (b s, 1H), 8.87 (s, 1H), 8.70 and 8.53 (b s, 1H), 8.22 (app d, J = 3.1,1H), 8.15 (b m, 1H), 7.94 (b m, 1H), 7.73 (b s, 1H), 7.48 (b m, 1H), 7.13 (app dd, J = 18.8, 9.9, 1H), 3.98 – 3.50 (b m, 8H); **LC/MS** (ES+) m/z (M+H)$^+$ = 449, HPLC R$_t$ = 1.220.
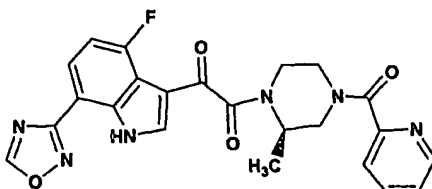
209

EXAMPLE 192

5   Purification was performed by preparative HPLC using the method: Start %B
     = 10, Final %B = 90, Gradient time = 15 min, Flow Rate = 40 ml/min, Column
     : YMC C18 S5 30 x 100mm, Fraction Collection: 10.26 – 10.71 min. ^{1}H NMR
     (CD$_3$OD) δ 9.40 (d, J = 3.5, 1H), 8.67 – 8.56 (b, m, 1H), 8.25 – 8.53 (b m,
     1H), 8.25 – 8.18 (b m,1H), 8.12 (b m, 1H), 8.03 (b m, 1H), 7.72 (b m, 1H),
10   7.60 (b m, 1H), 4.87 – 3.15 (b m, 7H), 1.42 and 1.27 (b m, 3H); LC/MS (ES+)
     m/z (M+H)$^+$ = 463, HPLC R$_t$ = 1.263.

EXAMPLE 193
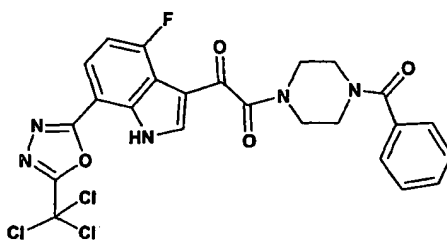
15

Purification was performed by preparative HPLC using the method: Start %B
= 30, Final %B = 100, Gradient time = 18 min, Flow Rate = 40 ml/min,
Column : YMC C18 S5 30 x 100mm, Fraction Collection: 15.58 – 16.18 min.
20   ^{1}H NMR (CDCl$_3$) δ 10.92 (s, 1H), 8.29 (d, J = 3.0, 1H), 7.99 (app dd, J = 8.0,
     4.0, 1H), 7.44 (b s, 5H), 7.18 (app t, J = 9.0, 1H), 3.98 – 3.52 (b m, 8H);
     LC/MS (ES+) m/z (M+H)$^+$ = 565, HPLC R$_t$ = 1.750.
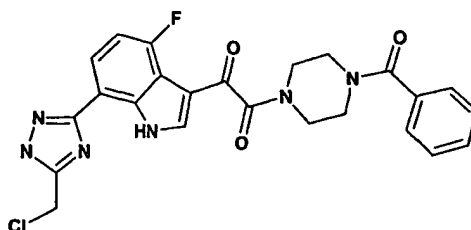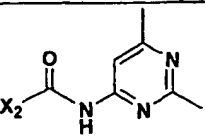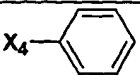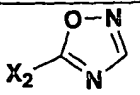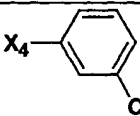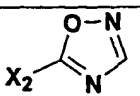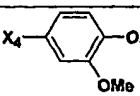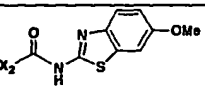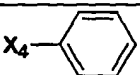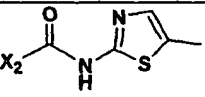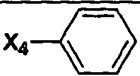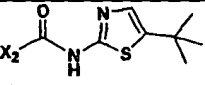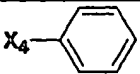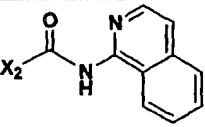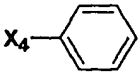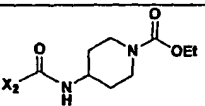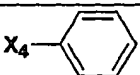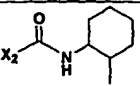
210

EXAMPLE 194

5   Purification was performed by preparative HPLC using the method: Start %B
= 20, Final %B = 80, Gradient time = 15 min, Flow Rate = 40 ml/min, Column
: YMC C18 S5 30 x 100mm, Fraction Collection: 11.57 – 11.87 min. ^{1}H NMR
(CDCl$_3$) δ 11.17 (s, 1H), 8.03 (s, 1H), 7.67 (app dd, J = 7.6, 3.9, 1H), 7.44 (b
s, 5H), 6.88 (app t, J = 9.3, 1H), 4.77 (s, 2H), 3.87 – 3.45 (b m, overlapping
10   with broad water peak, 8H); LC/MS (ES+) m/z (M+H)$^+$ = 495. HPLC R$_t$ =
1.380.

EXAMPLES 195-214

15   Compounds of Examples 195 to 214 were prepared according to the method
described in Scheme 25D and are of the general formula below.

211

EXAMPLE	R²	R⁵	R²⁰	A	HPLC R$_t$ (min)	(M+H)⁺
195	F	(1,2,4-oxadiazole linked via X_2; 3-position CH₂-SO₂-CH₂-(2-furyl))	H	X_4-phenyl	1.57	606.37
196	F	(1,2,4-oxadiazole linked via X_2; 3-position CH₂-S-(2-thienyl))	H	X_4-phenyl	1.742	576.32
197	F	(1,2,4-oxadiazole linked via X_2; 3-phenyl)	H	X_4-phenyl	1.428	524.25
198	F	(1,2,4-oxadiazole linked via X_2; 3-position CH₂-S-(2-pyridyl))	H	X_4-phenyl	1.563	571.36
199	F	(1,2,4-oxadiazole linked via X_2; 3-(4-fluorophenyl))	H	X_4-phenyl	1.527	542.15
200	F	(1,2,4-oxadiazole linked via X_2; 3-position CH₂-C(=O)-pyrrolidine)	H	X_4-phenyl	1.308	559.43
201	F	(1,2,4-oxadiazole linked via X_2; 3-benzyl)	H	X_4-phenyl	1.744	538.38
202	F	(1,2,4-oxadiazole linked via X_2; 3-(5-methyl-isoxazol-3-yl))	H	X_4-phenyl	1.360	529.14
203	F	(1,2,4-oxadiazole linked via X_2; 3-position CH₂CH₂-(3,5-dimethylpyrazol-1-yl))	H	X_4-phenyl	1.344	570.43
204	F	(X_2-C(=O)-NH-N-morpholine)	H	X_4-phenyl	1.036	508.21

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205	F		H		0.979	529.41
206	F		H		1.461	482.27
207	F		H		0.984	508.26
208	F		H		1.392	529.41
209	F		H		1.235	482.27
210	F		H		1.496	508.26
211	F		H		1.214	586.16
212	F		H		1.237	520.14
213	F		H		1.391	519.25
214	F		H		1.102	531.22

213

EXAMPLE 215

Special Procedures:
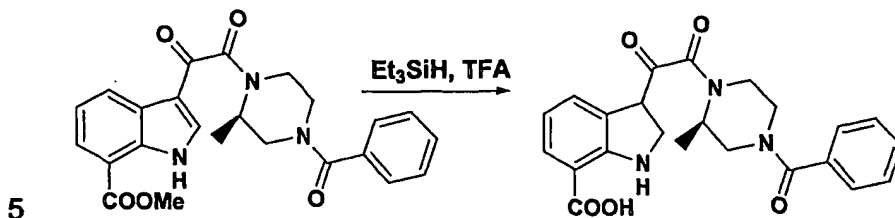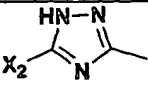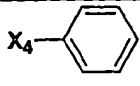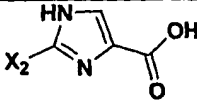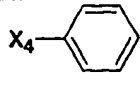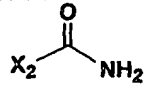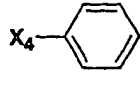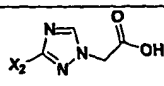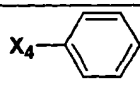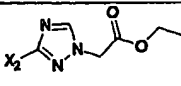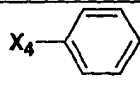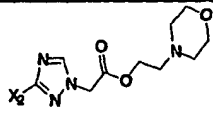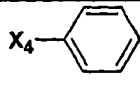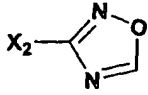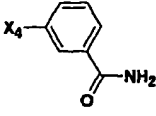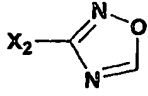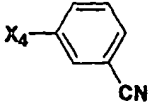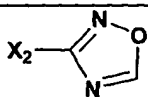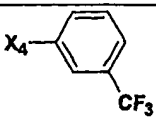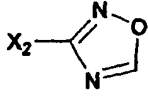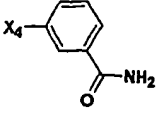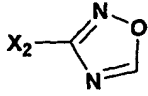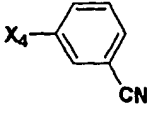
Preparation of 1-(benzoyl)-3-(R)-Methyl-4-[(7-hydoxycarbonyl-indolin-3-yl)-2-oxoacetyl]piperazine: 1-(benzoyl)-3-(R)-methyl-4-[(7-(methoxycarbonyl)indol-3-yl)-2-oxoacetyl]piperazine (50 mg) was dissolved in a solution of triethylsilane (Et₃SiH, 0.5 mL) in TFA (5 mL). The reaction was stirred for 10 hours. Solvents were removed under vaccum, and the residue was purified using Shimadzu automated preparative HPLC System to give 1-benzoyl-3-(R)-methyl-4-[(7-carboxyindolin-3-yl)-2-oxoacetyl]piperazine (5.5 mg).

Another aspect of the present invention are the compounds P-216 through P-280 in Table P-1 of the following general formula which may be prepared by the methods described herein.
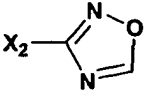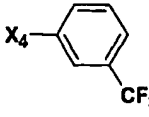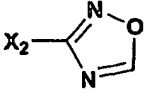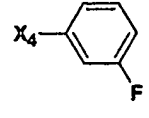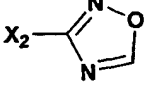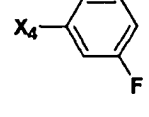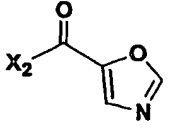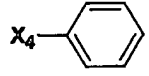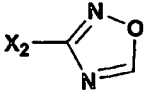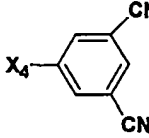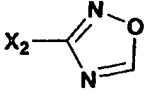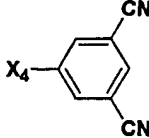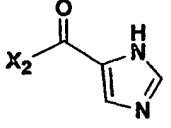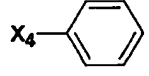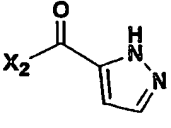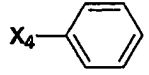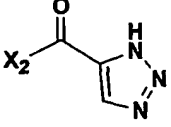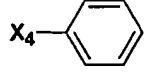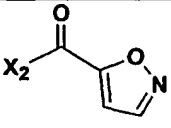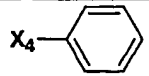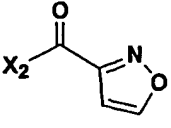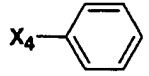
Table P-1
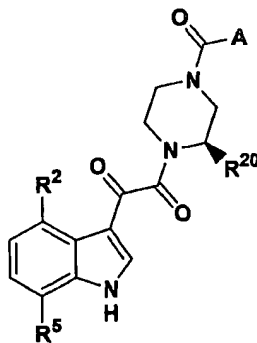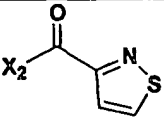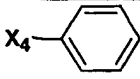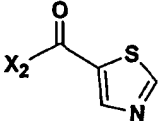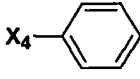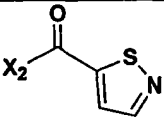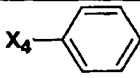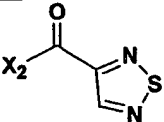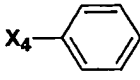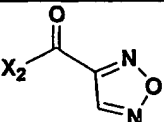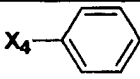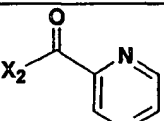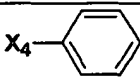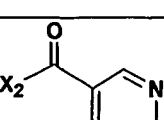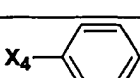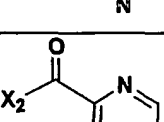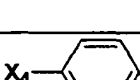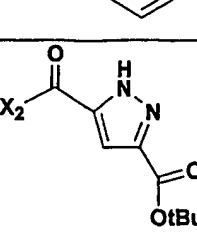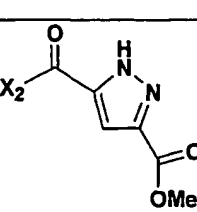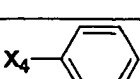
Compound	R²	R⁵	R²⁰	A
P-216	OCH₃		H	

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P-217	Cl		H	
P-218	F		H	
P-219	OCH$_3$		CH$_3$	
P-220	F		H	
P-221	F		H	
P-222	F		H	
P-223	F		H	
P-224	F		H	
P-225	F		H	
P-226	OCH$_3$		H	
P-227	OCH$_3$		H	
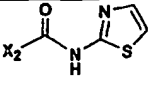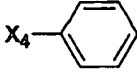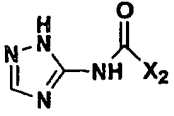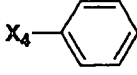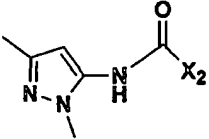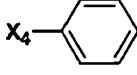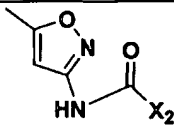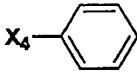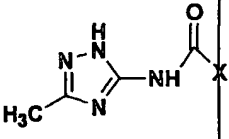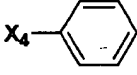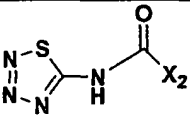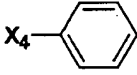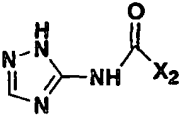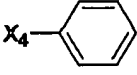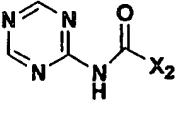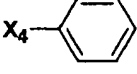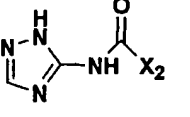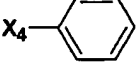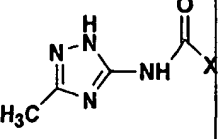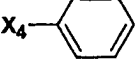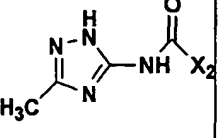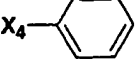
P-228	OCH₃	X₂-[1,2,4-oxadiazol-3-yl]	H	X₄-phenyl-CF₃
P-229	OCH₃	X₂-[1,2,4-oxadiazol-3-yl]	H	X₄-phenyl-F
P-230	F	X₂-[1,2,4-oxadiazol-3-yl]	H	X₄-phenyl-F
P-231	OCH₃	X₂-C(O)-[oxazol-5-yl]	H	X₄-phenyl
P-232	OCH₃	X₂-[1,2,4-oxadiazol-3-yl]	H	X₄-phenyl(CN)(CN)
P-233	F	X₂-[1,2,4-oxadiazol-3-yl]	H	X₄-phenyl(CN)(CN)
P-234	OCH₃	X₂-C(O)-[1H-imidazol-5-yl]	H	X₄-phenyl
P-235	OCH₃	X₂-C(O)-[1H-1,2,3-triazol-3-yl]	H	X₄-phenyl
P-236	OCH₃	X₂-C(O)-[1H-1,2,3-triazol-4-yl]	H	X₄-phenyl
P-237	OCH₃	X₂-C(O)-[isoxazol-5-yl]	H	X₄-phenyl
P-238	OCH₃	X₂-C(O)-[isoxazol-3-yl]	H	X₄-phenyl

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P-239	OCH$_3$		H	
P-240	OCH$_3$		H	
P-241	OCH$_3$		H	
P-242	OCH$_3$		H	
P-243	OCH$_3$		H	
P-244	OCH$_3$		H	
P-245	OCH$_3$		H	
P-246	OCH$_3$		H	
P-247	OCH$_3$		H	
P-248	OCH$_3$		H	
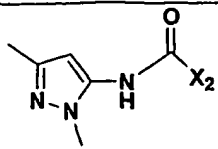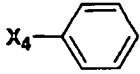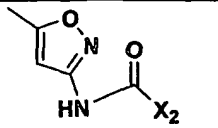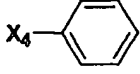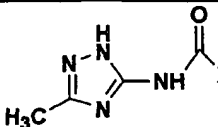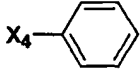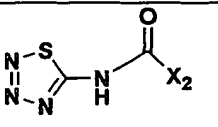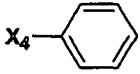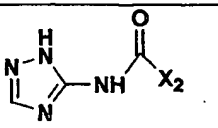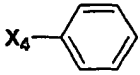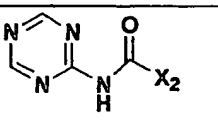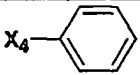
P-249	OCH₃		H	
P-250	OCH₃		H	
P-251	OCH₃		H	
P-252	F		H	
P-253	F		H	
P-254	F		H	
P-255	F		H	

P-256	F		H	
P-257	F		H	
P-258	OCH$_3$		H	
P-259	OCH$_3$		H	
P-260	OCH$_3$		H	
P-261	OCH$_3$		H	
P-262	OCH$_3$		H	
P-263	OCH$_3$		H	

P-264	OCH₃		H	
P-265	OCH₃		H	
P-266	OCH₃		H	
P-267	OCH₃		H	
P-268	OCH₃		H	
P-269	OCH₃		H	
P-270	OCH₃		H	
P-271	OCH₃		H	
P-272	F		H	
P-273	OCH₃		H	
P-274	F		H	

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P-275	F		H	
P-276	F		H	
P-277	F		H	
P-278	F		H	
P-279	F		H	
P-280	F		H	

Experimental Procedures

Biology

In Table I and hereafter, the following definitions apply.

- "µM" means micromolar;
- "ml" means milliliter;
- "µl" means microliter;
- "mg" means milligram;

The materials and experimental procedures used to obtain the results reported in Table I are described below.

Cells:

● <u>Virus production</u>-Human embryonic Kidney cell line, 293, propagated in Dulbecco's Modified Eagle Medium (Life Technologies, Gaithersburg, MD) containing 10% fetal Bovine serum (FBS, Sigma, St. Louis , MO).

● <u>Virus infection</u>- Human epithelial cell line, HeLa, expressing the HIV-1 receptors CD4 and CCR5 was propagated in Dulbecco's Modified Eagle Medium (Life Technologies, Gaithersburg, MD) containing 10% fetal Bovine serum (FBS, Sigma, St. Louis , MO) and supplemented with 0.2 mg/ml Geneticin (Life Technologies, Gaithersburg, MD) and 0.4 mg/ml Zeocin (Invitrogen, Carlsbad, CA).

Virus-Single-round infectious reporter virus was produced by co-transfecting human embryonic Kidney 293 cells with an HIV-1 envelope DNA expression vector and a proviral cDNA containing an envelope deletion mutation and the luciferase reporter gene inserted in place of HIV-1 nef sequences (Chen et al, Ref. 30b). Transfections were performed using lipofectAMINE PLUS reagent as described by the manufacturer (Life Technologies, Gaithersburg, MD).

Experiment

1. Compound was added to HeLa CD4 CCR5 cells plated in 96 well plates at a cell density of 5 X 10^4 cells per well in 100 µl Dulbecco's Modified Eagle Medium containing 10 % fetal Bovine serum at a concentration of <20 µM.

2. 100 µl of single-round infectious reporter virus in Dulbecco's Modified Eagle Medium was then added to the plated cells and compound at an approximate multiplicity of infection (MOI) of 0.01, resulting in a final volume of 200 µl per well and a final compound concentration of <10 µM.

3. Samples were harvested 72 hours after infection.

4. Viral infection was monitored by measuring luciferase expression from viral DNA in the infected cells using a luciferase reporter gene assay kit (Roche Molecular Biochemicals, Indianapolis, IN). Infected cell supernatants were removed and 50 µl of Dulbecco's Modified Eagle

5 Medium (without phenol red) and 50 µl of luciferase assay reagent reconstituted as described by the manufacturer (Roche Molecular Biochemicals, Indianapolis, IN) were added per well. Luciferase activity was then quantified by measuring luminescence using a Wallac microbeta scintillation counter.

10

5. The percent inhibition for each compound was calculated by quantifying the level of luciferase expression in cells infected in the presence of each compound as a percentage of that observed for cells infected in the absence of compound and subtracting such a determined value from 100.

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6. An EC_{50} provides a method for comparing the antiviral potency of the compounds of this invention. The effective concentration for fifty percent inhibition (EC_{50}) was calculated with the Microsoft Excel XLfit curve fitting software. For each compound, curves were generated from percent

20 inhibition calculated at 10 different concentrations by using a four paramenter logistic model (model 205). The EC_{50} data for the compounds is shown in Table 2. Table 1 is the key for the data in Table 2.

Results

25 Table 1. Biological Data Key for EC_{50}s

Compounds* with EC_{50}s >5µM	Compounds with EC_{50}s >1 µM but <5µM	Compounds with EC50 < 1 µM
Group C	Group B	Group A

*Some of these compounds may have been tested at a concentration lower than their EC_{50} but showed some ability to cause inhibition and thus should be evaluated at a higher concentration to determine the exact EC_{50}.

30

In Table 2, X_1, X_2, X_4 etc. indicates the point of attachment.
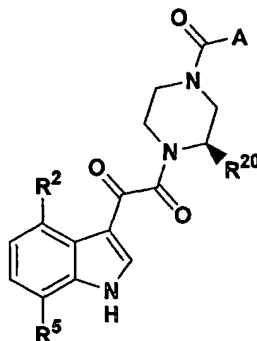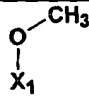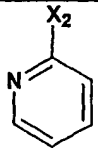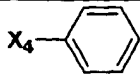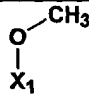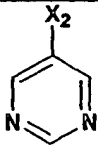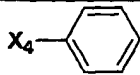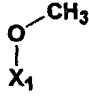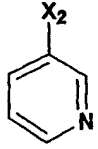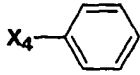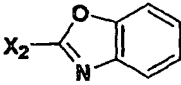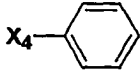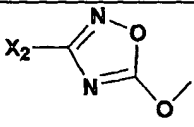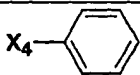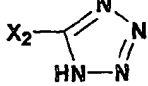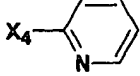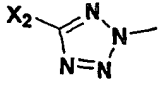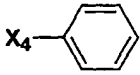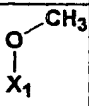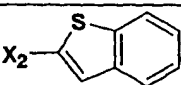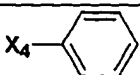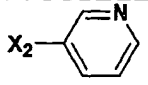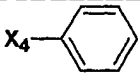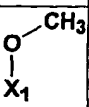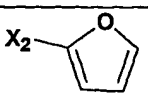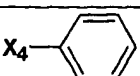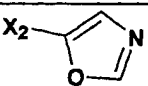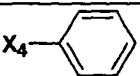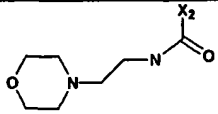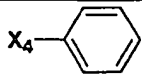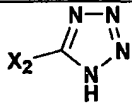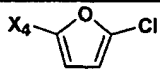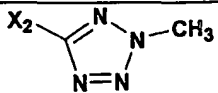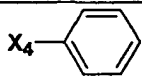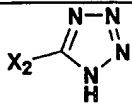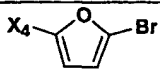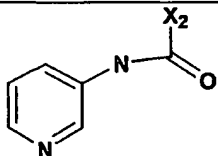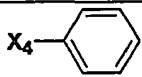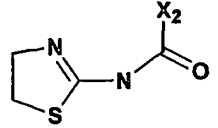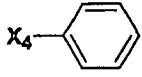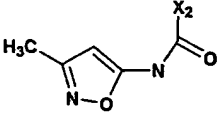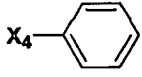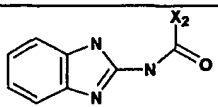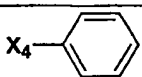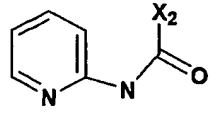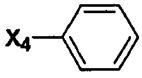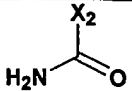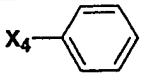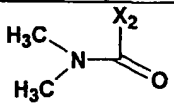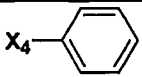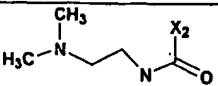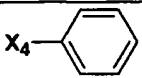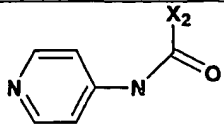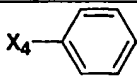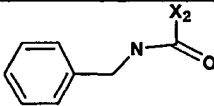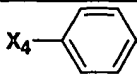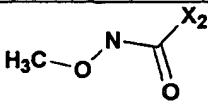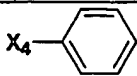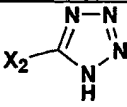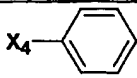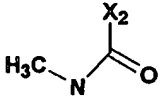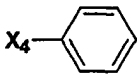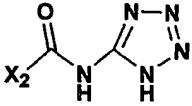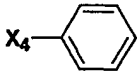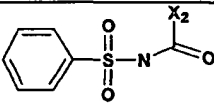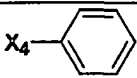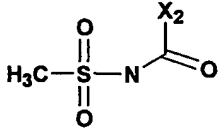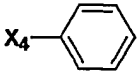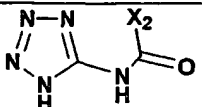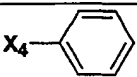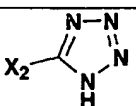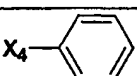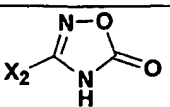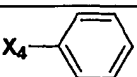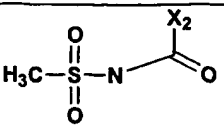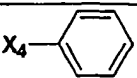
Table 2

Table Entry (Example number)	R²	R⁵	R²⁰	A	EC₅₀ Group from Table 1
1 (Example 1)	F	X₂—(phenyl)	H	X₄—(phenyl)	A
2 (Example 14)	F	X₂—(thiazol-2-yl)	H	X₄—(phenyl)	A
3 (Example 12)	F	X₂—(thiophen-2-yl)	H	X₄—(phenyl)	A
4 (Example 5)	F	X₂—(pyridin-2-yl)	H	X₄—(phenyl)	A
5 (Example 9)	F	X₂—(pyrimidin-5-yl)	H	X₄—(phenyl)	A
6 (Example 16)	F	X₂—(2-Cl-thiophen-5-yl)	H	X₄—(phenyl)	A
7 (Example 15)	O—CH₃ / X₁	X₂—(thiazol-2-yl)	H	X₄—(phenyl)	A

8 (Example 7)	O—CH₃ / X₁	X₂-pyridine (2-position)	H	X₄-phenyl	A
9 (Example 10)	O—CH₃ / X₁	X₂-pyrimidine	H	X₄-phenyl	A
10 (Example 8)	O—CH₃ / X₁	X₂-pyridine (3-position)	H	X₄-phenyl	A
11 (Example 18)	F	X₂-benzoxazole	H	X₄-phenyl	A
12 (Example 29)	F	X₂-(1,2,4-oxadiazole)-O-methyl	H	X₄-phenyl	A
13 (Example 34)	F	X₂-tetrazole (HN)	CH₃	X₄-pyridine	A
14 (Example 21)	F	X₂-tetrazole (N-methyl)	H	X₄-phenyl	A
15 (Example 19)	O—CH₃ / X₁	X₂-benzothiophene	H	X₄-phenyl	A
16 (Example 6)	F	X₂-pyridine	H	X₄-phenyl	A
17 (Example 11)	O—CH₃ / X₁	X₂-furan	H	X₄-phenyl	A
18 (Example 17)	F	X₂-oxazole	H	X₄-phenyl	A
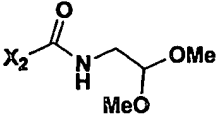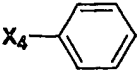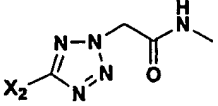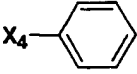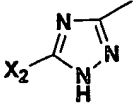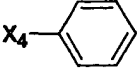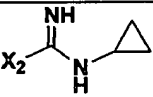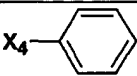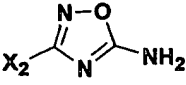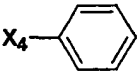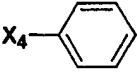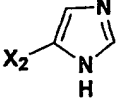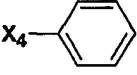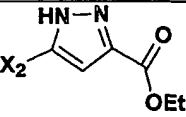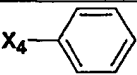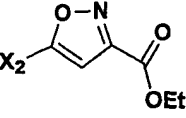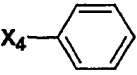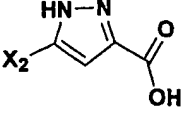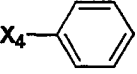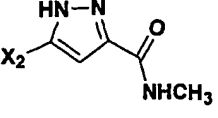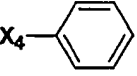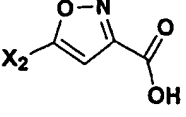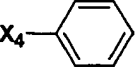
19 (Example 30)	F		H		A
20 (Example 31)	F		H		A
21 (Example 4)	F		H		A
22 (Example 13)	F		H		A
23 (Example 26)	F		H		A
24 (Example 3)			H		A
25 (Example 2)	F		H		A
26 (Example 167)	F		H		A
27 (Example 170)	F		H		A
28 (Example 24)	F		H		A
29 (Example 23)	F		H		A
30 (Example 25)	F		H		A

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31 (Example 22)	F	X₂–tetrazole–CH₂–C(=O)–O–CH₃	H	X₄–phenyl	A
32 (Example 173)	F	X₂–tetrazole(N–CH₃)	H	X₄–furan–Br	A
33 (Example 172)	F	X₂–tetrazole(N–CH₃)	H	X₄–furan–Cl	A
34 (Example 171)	F	X₂–tetrazole(N–CH₃)	H	X₄–furan	A
35 (Example 174)	F	X₂–tetrazole(N–CH₃)	H	X₄–thiophene	A
36 (Example 40)	F	phenyl–SO₂–N(H)–C(=O)–X₂	H	X₄–phenyl	A
37 (Example 32)	F	X₂–tetrazole(NH)	H	X₄–pyridine	A
38 (Example 185A)	F	H₂N–C(X₂)=N–OH	CH₃	X₄–phenyl	A
39 (Example 186A)	F	X₂–C(=O)–NH₂	CH₃	X₄–phenyl	A
40 (Example 49)	F	imidazole–CH₂CH₂–N(H)–C(=O)–X₂	H	X₄–phenyl	A
41 (Example 48)	F	indole–CH₂CH₂–N(H)–C(=O)–X₂	H	X₄–phenyl	A
42 (Example 50)	F	furan–CH₂–N(H)–C(=O)–X₂	H	X₄–phenyl	A
43 (Example 51)	F	thiophene–CH₂–N(H)–C(=O)–X₂	H	X₄–phenyl	A

No. (Example)		X2 group		X4 group	A
44 (Example 52)	F	morpholine-CH₂CH₂-NH-C(=O)-X₂	H	X₄-phenyl	A
45 (Example 168)	F	X₂-tetrazole (NH)	H	X₄-furan-Cl	A
46 (Example)	F	X₂-tetrazole-N-CH₃	CH₃	X₄-phenyl	A
47 (Example 169)	F	X₂-tetrazole (NH)	H	X₄-furan-Br	A
48 (Example 35)	F	pyridin-3-yl-NH-C(=O)-X₂	H	X₄-phenyl	A
49 (Example 36)	F	4,5-dihydrothiazol-2-yl-NH-C(=O)-X₂	H	X₄-phenyl	A
50 (Example 37)	F	3-methylisoxazol-5-yl-NH-C(=O)-X₂	H	X₄-phenyl	A
51 (Example 41)	F	benzimidazol-2-yl-NH-C(=O)-X₂	H	X₄-phenyl	A
52 (Example 38)	F	pyridin-2-yl-NH-C(=O)-X₂	H	X₄-phenyl	A
53 (Example 42)	F	H₂N-C(=O)-X₂	H	X₄-phenyl	A
54 (Example 43)	F	(H₃C)₂N-C(=O)-X₂	H	X₄-phenyl	A
55 (Example 44)	F	(H₃C)(CH₃)N-CH₂CH₂-NH-C(=O)-X₂	H	X₄-phenyl	A

56 (Example 39)	F	pyridin-4-yl–NH–C(=O)–X₂	H	X₄–phenyl	A
57 (Example 45)	F	phenyl–CH₂–N–C(=O)–X₂	H	X₄–phenyl	A
58 (Example 46)	F	H₃C–O–N–C(=O)–X₂	H	X₄–phenyl	A
59 (Example 33)	F	X₂–(1H-tetrazol-5-yl)	CH₃	X₄–phenyl	A
60 (Example 47)	F	H₃C–N–C(=O)–X₂	H	X₄–phenyl	A
61 (Example 54)	F	X₂–C(=O)–NH–(1H-tetrazol-5-yl)	H	X₄–phenyl	A
62 (Example 62)	H	phenyl–SO₂–N–C(=O)–X₂	H	X₄–phenyl	B
63 (Example 61)	H	H₃C–SO₂–N–C(=O)–X₂	H	X₄–phenyl	B
64 (Example 63)	H	(1H-tetrazol-5-yl)–NH–C(=O)–X₂	H	X₄–phenyl	A
65 (Example 20)	F	X₂–(1H-tetrazol-5-yl)	H	X₄–phenyl	A
66 (Example 28)	F	X₂–(1,2,4-oxadiazol-5(4H)-one)	H	X₄–phenyl	A
67 (Example 60)	F	H₃C–SO₂–N–C(=O)–X₂	H	X₄–phenyl	A

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68 (Example 27)	F	X_2, H_2N—C=N—OH (amidoxime)	H	X_4-phenyl	A
69 (Example 69)	F	X_2—C(O)—N-piperazine-N—C(O)—phenyl	H	X_4-phenyl	A
70 (Example 64)	H	CH$_3$—HN—C(O)—X_2	CH$_3$	X_4-phenyl	A
71 (Example 65)	H	(CH$_3$)$_2$N—C(O)—X_2	CH$_3$	X_4-phenyl	A
72 (Example 67)	H	ethyl—NH—C(O)—X_2	CH$_3$	X_4-phenyl	A
73 (Example 66)	H	(ethyl)$_2$N—CH$_2$CH$_2$—N—C(O)—X_2	CH$_3$	X_4-phenyl	A
74 (Example 68)	H	benzyl-piperazine-N—C(O)—X_2	CH$_3$	X_4-phenyl	A
75 (Example 73)	F	X_2-oxazole	H	X_4-phenyl	A
76 (Example 70)	F	X_2-tetrazole-CH$_2$-C(O)OH	H	X_4-phenyl	A
77 (Example 76)	F	X_2-benzimidazole	H	X_4-phenyl	A
78 (Example 80)	F	X_2-(5-methyl-1,2,4-oxadiazol-3-yl)	H	X_4-phenyl	A
79 (Example 79)	F	X_2-(1,2,4-oxadiazol-3-yl)	H	X_4-phenyl	A
80 (Example 82)	F	X_2-(5-(cyclopropylamino)-1,2,4-oxadiazol-3-yl)	H	X_4-phenyl	A

81 (Example 72)	F		H		A
82 (Example 71)	F		H		A
83 (Example 78)	F		H		A
84 (Example 75)	F		H		A
85 (Example 83)	F		H		A
86 (Example 84)	F		H		A
87 (Example 85)	F		H		A
88 (Example 86)	F		H		A
89 (Example 87)	F		H		A
90 (Example 88)	F		H		A
91 (Example 89)	F		H		A
92 (Example 90)	F		H		A
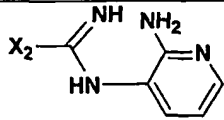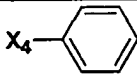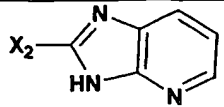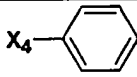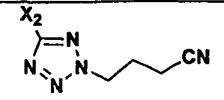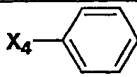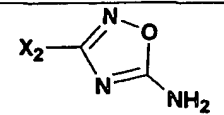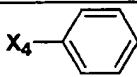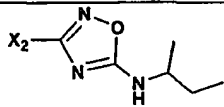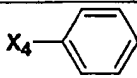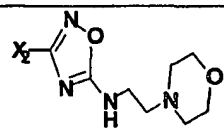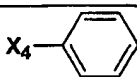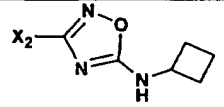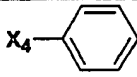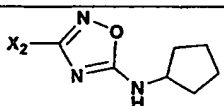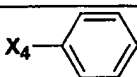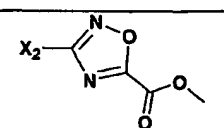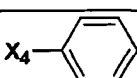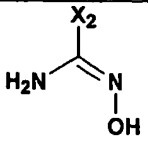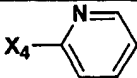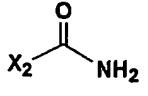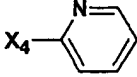
93 (Example 91)	F		H		A
94 (Example 92)	F		H		A
95 (Example 93)	F		H		A
96 (Example 94)	F		H		A
97 (Example 95)	F		H		A
98 (Example 96)	F		H		A
99 (Example 97)	F		H		A
100 (Example 98)	F		H		A
101 (Example 99)	F		H		A
102 (Example 100)	F		H		A
103 (Example 101)	F		H		A
104 (Example 102)	F		H		A
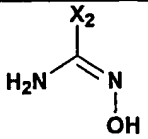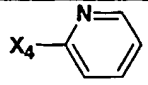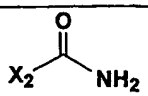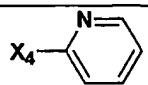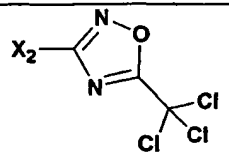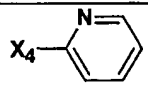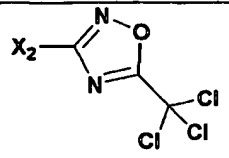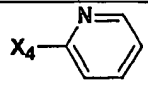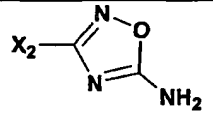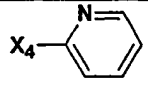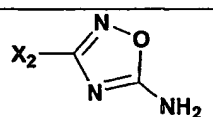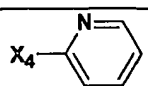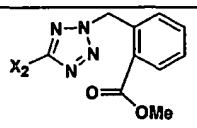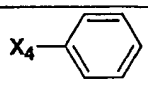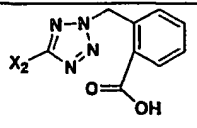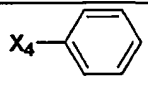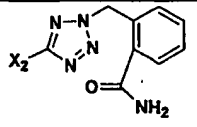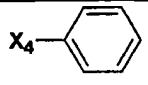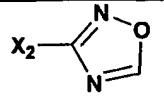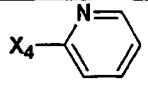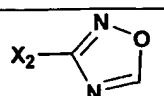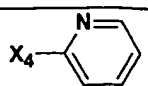
105 (Example 103)	F		H	X₄—	A
106 (Example 104)	F		H	X₄—	A
107 (Example 105A)	F		H	X₄—	A
108 (Example 106A)	F		H	X₄—	A
109 (Example 107A)	F		H	X₄—	A
110 (Example 108)	F		H	X₄—	A
111 (Example 53)	F		H	X₄—	A
112 (Example 55)	F		H	X₄—	A
113 (Example 56)	F		H	X₄—	A
114 (Example 57)	F		H	X₄—	A
115 (Example 58)	F		H	X₄—	A

No.					
116 (Example 59)	F		H	X4—phenyl	A
117 (Example 72)	F	X2-C(O)-N(H)-CH2-C(OMe)(OMe)	H	X4—phenyl	A
118 (Example 81)	F	X2—(1,2,4-oxadiazole)-CCl3	H	X4—phenyl	A
119 (Example 111)	F	X2—(1,2,4-triazole)NH	H	X4—phenyl	A
120 (Example 176)	F	X2—(1,2,4-oxadiazol-5(4H)-one)	CH3	X4—phenyl	A
121 (Example 177)	F	morpholine-CH2CH2-N-C(O)-X2	CH3	X4—phenyl	A
122 (Example 178)	F	X2—(1,2,4-oxadiazole)-CH3	CH3	X4—phenyl	A
123 (Example 114)	F	X2—(tetrazole)-CH2CH2-N(Et)2	H	X4—phenyl	A
124 (Example 113)	F	X2—(tetrazole)-CH2CH2-(isoindole-1,3-dione)	H	X4—phenyl	A
125 (Example 179)	F	X2—(1,2,4-oxadiazole)-cyclopropyl	CH3	X4—phenyl	A
126 (Example 149)	F	X2—(tetrazole)-CHF2	H	X4—pyridyl	A

127 (Example 180)	F		CH₃		A
128 (Example 153)	F		H		A
129 (Example 154)	F		H		A
130 (Example 181)	F		CH₃		A
131 (Example 152)	F		H		A
132 (Example 112)	F		H		A
133 (Example 163)	F		H		A
134 (Example 164)	F		H		A
135 (Example 156)	F		H		A
136 (Example 157)	F		H		A
137 (Example 158)	F		H		A

No. (Example)		Structure (X_2)		Structure (X_4)	A
138 (Example 166)	F	X_2—C(=NH)—NH— pyridine with NH_2	H	X_4-phenyl	A
139 (Example 165)	F	X_2—imidazo[4,5-b]pyridine (NH)	H	X_4-phenyl	A
140 (Example 115)	F	X_2—tetrazole—CH$_2$CH$_2$CN	H	X_4-phenyl	A
141 (Example 155)	F	X_2—1,2,4-oxadiazole—NH_2	CH$_3$	X_4-phenyl	A
142 (Example 160)	F	X_2—1,2,4-oxadiazole—NH—CH(CH$_3$)CH$_2$CH$_3$	CH$_3$	X_4-phenyl	A
143 (Example 159)	F	X_2—1,2,4-oxadiazole—NH—CH$_2$CH$_2$—morpholine(O)	CH$_3$	X_4-phenyl	A
144 (Example 161)	F	X_2—1,2,4-oxadiazole—NH—cyclobutyl	CH$_3$	X_4-phenyl	A
145 (Example 162)	F	X_2—1,2,4-oxadiazole—NH—cyclopentyl	CH$_3$	X_4-phenyl	A
146 (Example 182)	F	X_2—1,2,4-oxadiazole—C(=O)—O—CH$_3$	CH$_3$	X_4-phenyl	A
147 (Example 183)	F	X_2—C(NH$_2$)=N—OH	H	X_4-pyridine (N=)	A
148 (Example 184)	F	X_2—C(=O)—NH$_2$	H	X_4-pyridine (N=)	A

149 (Example 185B)	F	X_2—C(=N—OH)—NH$_2$ (hydroxyamidine)	CH$_3$	X_4—(pyridin-2-yl)	A
150 (Example 186B)	F	X_2—C(=O)—NH$_2$	CH$_3$	X_4—(pyridin-2-yl)	A
151 (Example 187)	F	X_2—(1,2,4-oxadiazol-3-yl)—CCl$_3$	CH$_3$	X_4—(pyridin-2-yl)	A
152 (Example 188)	F	X_2—(1,2,4-oxadiazol-3-yl)—CCl$_3$	H	X_4—(pyridin-2-yl)	A
153 (Example 189)	F	X_2—(1,2,4-oxadiazol-3-yl)—NH$_2$	H	X_4—(pyridin-2-yl)	A
154 (Example 190)	F	X_2—(1,2,4-oxadiazol-3-yl)—NH$_2$	CH$_3$	X_4—(pyridin-2-yl)	A
155 (Example 105B)	F	X_2—(tetrazol-5-yl)—N—CH$_2$—(2-(CO$_2$Me)phenyl)	H	X_4—phenyl	A
156 (Example 106B)	F	X_2—(tetrazol-5-yl)—N—CH$_2$—(2-(CO$_2$H)phenyl)	H	X_4—phenyl	A
157 (Example 107B)	F	X_2—(tetrazol-5-yl)—N—CH$_2$—(2-(C(=O)NH$_2$)phenyl)	H	X_4—phenyl	A
158 (Example 191)	F	X_2—(1,2,4-oxadiazol-3-yl)	H	X_4—(pyridin-2-yl)	A
159 (Example 192)	F	X_2—(1,2,4-oxadiazol-3-yl)	CH$_3$	X_4—(pyridin-2-yl)	A

160 (Example 193)	F		H		A
161 (Example 125)			H		A
162 (Example 140)	F		H		A
163 (Example 124)			H		A
164 (Example 106C)	F		H		A
165 (Example 105C)	F		H		A
166 (Example 107C)	F		H		A
167 (Example 141)	F		H		A
168 (Example 142)	F		H		A
169 (Example 143)	F		H		A
170 (Example 121)	F		H		A

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171 (Example 136)	F		H		A
172 (Example 137)	F		H		A
173 (Example 122)	F		H	X₄—O—	A
174 (Example 148)			H		A
175 (Example 138)	F		H		A
176 (Example 110A)	F		H		A
177 (Example 139)	F		H		A
178 (Example 132)	F		H		A
179 (Example 194)	F		H		A
180 (Example 146)	F		H		A
181 (Example 126)			H		A
182 (Example 134)	F		H		A
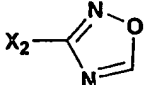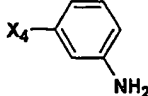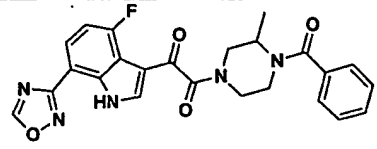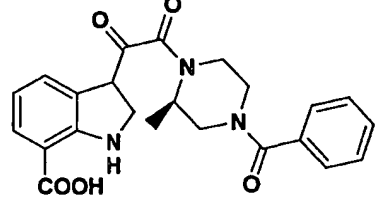
183 (Example 135)	F		H		A
184 (Example 133)	F		H		A
185 (Example 129)	F		H		A
186 (Example 127)	F		H		A
187 (Example 130)	F		H		A
188 (Example 147)	F		H		A
189 (Example 128)	F		H		A
190 (Example 119)	O-CH₃ | X₁		H		A
191 (Example 120)	F		H		A
192 (Example 116)	F		H		A
193 (Example 117)	F		H		A
194 (Example 131)	F		H		A

195 (Example 118)	F		H		A
196 (Example 144)	F		H		A
197 (Example 150)	F		H		A
198 (Example 195)	F		H		A
199 (Example 196)	F		H		A
200 (Example 197)	F		H		A
201 (Example 198)	F		H		A
202 (Example 199)	F		H		A
203 (Example 200)	F		H		A
204 (Example 201)	F		H		A
205 (Example 202)	F		H		A
206 (Example 203)	F		H		A

207 (Example 204)	F	X₂—C(=O)—NH—N(morpholine)	H	X₄—phenyl	A
208 (Example 205)	F	X₂—C(=O)—NH—(2,6-dimethylpyrimidin-4-yl)	H	X₄—phenyl	A
209 (Example 206)	F	X₂—(1,2,4-oxadiazol-5-yl)	H	X₄—(3-Cl-phenyl)	A
210 (Example 207)	F	X₂—(1,2,4-oxadiazol-5-yl)	H	X₄—(3,4-di-OMe-phenyl)	A
211 (Example 208)	F	X₂—C(=O)—NH—(6-OMe-benzothiazol-2-yl)	H	X₄—phenyl	A
212 (Example 209)	F	X₂—C(=O)—NH—(5-methylthiazol-2-yl)	H	X₄—phenyl	A
213 (Example 210)	F	X₂—C(=O)—NH—(5-tert-butylthiazol-2-yl)	H	X₄—phenyl	A
214 (Example 211)	F	X₂—C(=O)—NH—(isoquinolin-1-yl)	H	X₄—phenyl	A
215 (Example 212)	F	X₂—C(=O)—NH—(1-(ethoxycarbonyl)piperidin-4-yl)	H	X₄—phenyl	A
216 (Example 213)	F	X₂—C(=O)—NH—(2-methylcyclohexyl)	H	X₄—phenyl	A
217 (Example 214)	F	X₂—C(=O)—NH—(1,3,5-trimethylpyrazol-4-yl)	H	X₄—phenyl	A
219 (Example 145)	F	X₂—(1,2,4-triazol-1-yl)—CH₂—C(=O)—NH—CH₃	H	X₄—phenyl	

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220 (Example 151)	F	X₂ oxadiazole structure	H	X₄ aniline structure	

(Example 123)	indole structure with oxadiazole	A

(Example 215)	indoline structure	A

The compounds of Table 3 below were all found to be very potent in the assay described above using % inhibition as a criteria. In Table 3, X_2, X_4 etc. indicates the point of attachment. The vast majority of the compounds exhibited greater than 98% inhibition at a concentration of 10uM. The data at 10μM was calculated in the following manner:

Method for extrapolating % inhibition at 10μM

The data in Table 3 was obtained using the general procedures above and by the following methods. Data is not reported for all compounds since data for all the compounds is reported by the alternate method in Table 2. The percent inhibition for each compound was calculated by quantifying the level of luciferase expression in cells infected in the presence of compound as a percentage of that observed for cells infected in the absence of compound and subtracting such a determined value from 100. For compounds tested at concentrations less than 10 μM, the percent inhibition at 10 μM was determined by extrapolation using the XLfit curve fitting feature of the Microsoft Excel spreadsheet software. Curves were obtained from 10 data points (% inhibition determined at 10 concentrations of compound) by using a four parameter logistic model (XLfit model 205: $y = A + ((B-A)/(1+((C/x)^D)))$, where, A = minimum y, B = maximum y, C = $logEC_{50}$, D =

slope factor, and x and y are known data values. Extrapolations were performed with the A and B parameters unlocked.

     Thus the compounds of this invention are all potent antiviral inhibitors
5   based on this assay.

Table 3
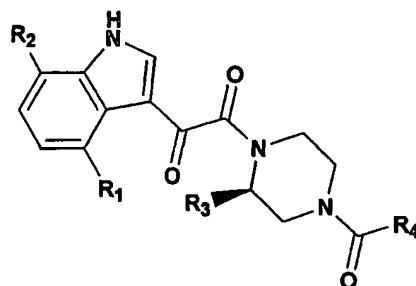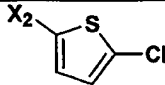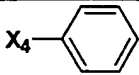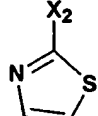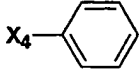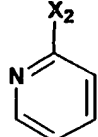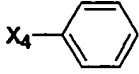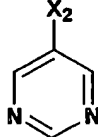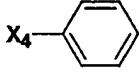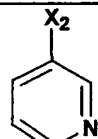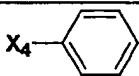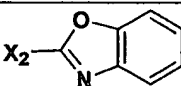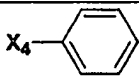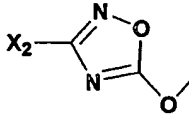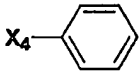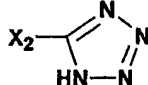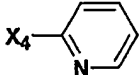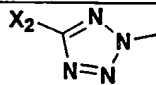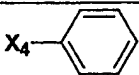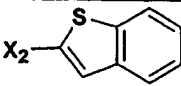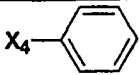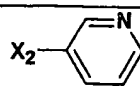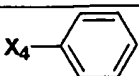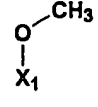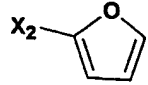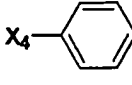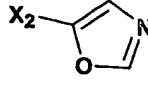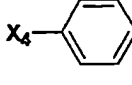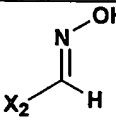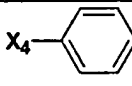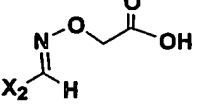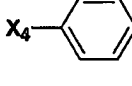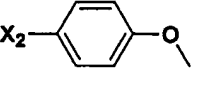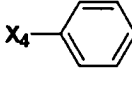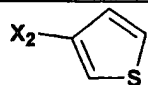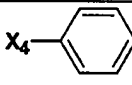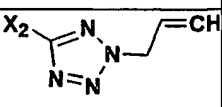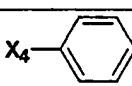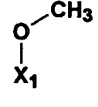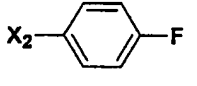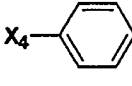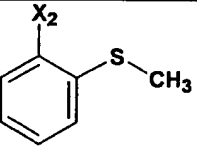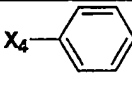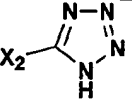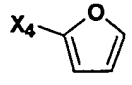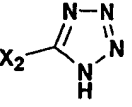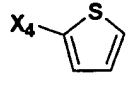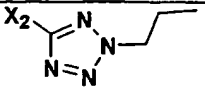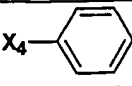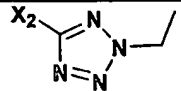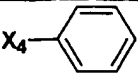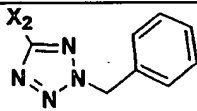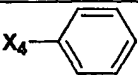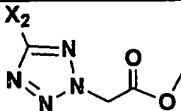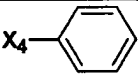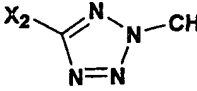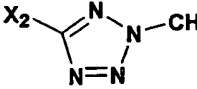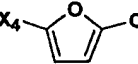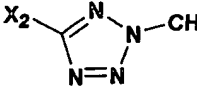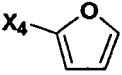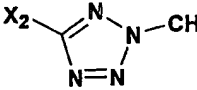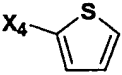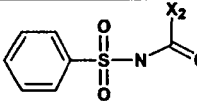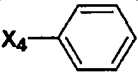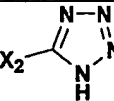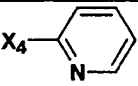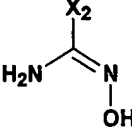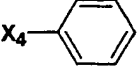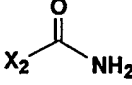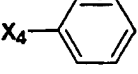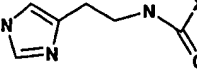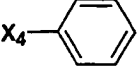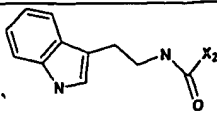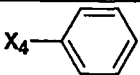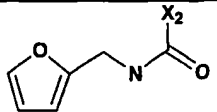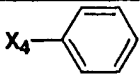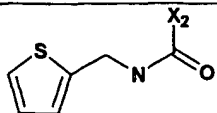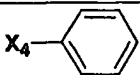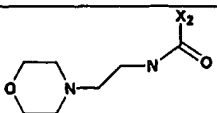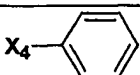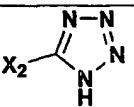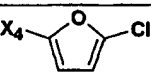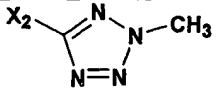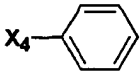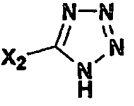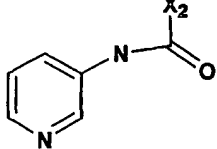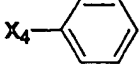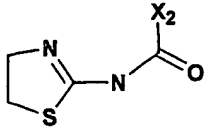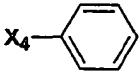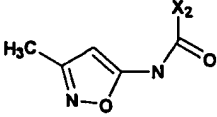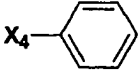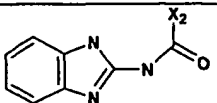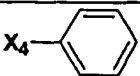
Table Entry (Example number)	R1	R2	R3	R4	% Inhibition @ 10 uM
1 (Example 1)	F	X₂—⟨phenyl⟩	H	X₄—⟨phenyl⟩	>98
2 (Example 14)	F	X₂—⟨thiazole⟩	H	X₄—⟨phenyl⟩	>98
3 (Example 12)	F	X₂—⟨thiophene⟩	H	X₄—⟨phenyl⟩	>98
4 (Example 5)	F	X₂—⟨pyridine⟩	H	X₄—⟨phenyl⟩	>98
5 (Example 9)	F	X₂—⟨pyrimidine⟩	H	X₄—⟨phenyl⟩	>98

6 (Example 16)	F	X_2 — thiophene-Cl	H	X_4 — phenyl	>98
7 (Example 15)	$O{-}CH_3$ on X_1	X_2 — thiazole	H	X_4 — phenyl	>98
8 (Example 7)	$O{-}CH_3$ on X_1	X_2 — pyridine	H	X_4 — phenyl	>98
9 (Example 10)	$O{-}CH_3$ on X_1	X_2 — pyrimidine	H	X_4 — phenyl	>98
10 (Example 8)	$O{-}CH_3$ on X_1	X_2 — pyridine	H	X_4 — phenyl	>98
11 (Example 18)	F	X_2 — benzoxazole	H	X_4 — phenyl	>98
12 (Example 29)	F	X_2 — oxadiazole-O	H	X_4 — phenyl	>98
13 (Example 34)	F	X_2 — tetrazole (HN)	CH_3	X_4 — pyridine	>98
14 (Example 21)	F	X_2 — tetrazole N-CH3	H	X_4 — phenyl	>98
15 (Example 19)	$O{-}CH_3$ on X_1	X_2 — benzothiophene	H	X_4 — phenyl	>98
16 (Example 6)	F	X_2 — pyridine	H	X_4 — phenyl	>98

No.	X₁	X₂		X₄	
17 (Example 11)	O–CH₃ (O–X₁)	(2-furyl)	H	(phenyl)	>98
18 (Example 17)	F	(oxazol-5-yl)	H	(phenyl)	>98
19 (Example 30)	F	(CH=N–OH)	H	(phenyl)	>98
20 (Example 31)	F	(CH=N–O–CH₂–COOH)	H	(phenyl)	>98
21 (Example 4)	F	(4-methoxyphenyl)	H	(phenyl)	>98
22 (Example 13)	F	(thiophen-3-yl)	H	(phenyl)	>98
23 (Example 26)	F	(tetrazol-2-yl, N–CH₂–CH=CH)	H	(phenyl)	>98
24 (Example 3)	O–CH₃ (O–X₁)	(4-fluorophenyl)	H	(phenyl)	>98
25 (Example 2)	F	(2-(methylthio)phenyl)	H	(phenyl)	>98
26 (Example 167)	F	(tetrazol-5-yl, NH)	H	(2-furyl)	>98
27 (Example 170)	F	(tetrazol-5-yl, NH)	H	(thiophen-2-yl)	>98
28 (Example 24)	F	(tetrazol-2-yl, N–CH₂–CH₂–CH₃)	H	(phenyl)	>98

29 (Example 23)	F	X2-tetrazole-N-ethyl	H	X4-phenyl	>98
30 (Example 25)	F	X2-tetrazole-N-benzyl	H	X4-phenyl	>98
31 (Example 22)	F	X2-tetrazole-N-CH2C(O)O	H	X4-phenyl	>98
32 (Example 173)	F	X2-tetrazole-N-CH3	H	X4-furan-Br	>98
33 (Example 172)	F	X2-tetrazole-N-CH3	H	X4-furan-Cl	>98
34 (Example 171)	F	X2-tetrazole-N-CH3	H	X4-furan	>98
35 (Example 174)	F	X2-tetrazole-N-CH3	H	X4-thiophene	>98
36 (Example 40)	F	phenyl-SO2-N-C(O)-X2	H	X4-phenyl	>98
37 (Example 32)	F	X2-tetrazole-NH	H	X4-pyridine	>98
38 (Example 185A)	F	X2-C(=N-OH)-NH2	CH3	X4-phenyl	>98
39 (Example 186A)	F	X2-C(O)-NH2	CH3	X4-phenyl	>98
40 (Example 49)	F	imidazole-CH2CH2-N-C(O)-X2	H	X4-phenyl	>98

41 (Example 48)	F		H	X_4—phenyl	>98
42 (Example 50)	F		H	X_4—phenyl	>98
43 (Example 51)	F		H	X_4—phenyl	>98
44 (Example 52)	F		H	X_4—phenyl	>98
45 (Example 168)	F	X_2—tetrazole	H	X_4—furan—Cl	>98
46 (Example 175)	F	X_2—tetrazole—CH_3	CH_3	X_4—phenyl	>98
47 (Example 169)	F	X_2—tetrazole	H	X_4—furan—Br	>98
48 (Example 35)	F		H	X_4—phenyl	>98
49 (Example 36)	F		H	X_4—phenyl	>98
50 (Example 37)	F		H	X_4—phenyl	>98
51 (Example 41)	F		H	X_4—phenyl	>98

No (Example)		Structure			Value
52 (Example 38)	F		H	X₄—phenyl	>98
53 (Example 42)	F		H	X₄—phenyl	>98
54 (Example 43)	F		H	X₄—phenyl	89
55 (Example 44)	F		H	X₄—phenyl	97
56 (Example 39)	F		H	X₄—phenyl	>98
57 (Example 45)	F		H	X₄—phenyl	>98
58 (Example 46)	F		H	X₄—phenyl	>98
59 (Example 33)	F		CH₃	X₄—phenyl	>98
60 (Example 47)	F		H	X₄—phenyl	>98
61 (Example 54)	F		H	X₄—phenyl	>98
62 (Example 29)	F		H	X₄—phenyl	>98
63 (Example 62)	H		H	X₄—phenyl	74

No.		Structure			
64 (Example 61)	H	$H_3C-SO_2-N-C(=O)-X_2$	H	X_4—phenyl	75
65 (Example 63)	H	tetrazole–NH–C(=O)–X_2	H	X_4—phenyl	96
66 (Example 20)	F	tetrazole–X_2	H	X_4—phenyl	>98
67 (Example 28)	F	1,2,4-oxadiazol-5(4H)-one–X_2	H	X_4—phenyl	>98
68 (Example 60)	F	$H_3C-SO_2-N-C(=O)-X_2$	H	X_4—phenyl	>98
69 (Example 27)	F	$H_2N-C(=N-OH)-X_2$	H	X_4—phenyl	>98
70 (Example 69)	F	$X_2-C(=O)-N$-piperazine-$N-C(=O)$-phenyl	H	X_4—phenyl	>98
71 (Example 64)	H	$CH_3-HN-C(=O)-X_2$	CH_3	X_4—phenyl	>98
72 (Example 65)	H	$(CH_3)_2N-C(=O)-X_2$	CH_3	X_4—phenyl	70
73 (Example 67)	H	ethyl-NH-C(=O)-X_2	CH_3	X_4—phenyl	>98
74 (Example 66)	H	diethyl-N-CH$_2$CH$_2$-NH-C(=O)-X_2	CH_3	X_4—phenyl	98
75 (Example 68)	H	benzyl-N-piperazine-$N-C(=O)-X_2$	CH_3	X_4—phenyl	>98

76 (Example 73)	F		H		>98
77 (Example 70)	F		H		>98
78 (Example 76)	F		H		>98
79 (Example 80)	F		H		>98
80 (Example 79)	F		H		>98
81 (Example 82)	F		H		>98
82 (Example 72)	F		H		>98
83 (Example 71)	F		H		>98
84 (Example 77)	F		H		>98
85 (Example 75)	F		H		>98
86 (Example 83)	F		H		>98

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The compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic
5   pharmaceutically-acceptable carriers, adjuvants and vehicles.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating viral infections such as HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical
10   composition comprising a pharmaceutical carrier and a therapeutically-effective amount of a compound of the present invention.

The pharmaceutical composition may be in the form of orally-administrable suspensions or tablets; nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous
15   suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a
20   viscosity enhancer, and sweetners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

25   The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic
30   mono- or diglycerides, and fatty acids, including oleic acid.

The compounds of this invention can be administered orally to humans in a dosage range of 1 to 100 mg/kg body weight in divided doses. One preferred dosage range is 1 to 10 mg/kg body weight orally in divided

doses. Another preferred dosage range is 1 to 20 mg/kg body weight orally in divided doses. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific

5   compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

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CLAIMS

What is claimed is:

1. A compound of Formula I, including pharmaceutically acceptable salts
5 thereof,

I
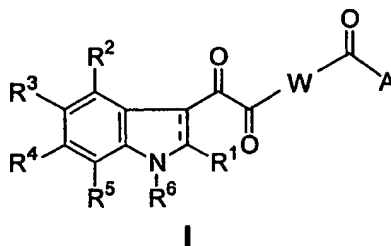
10 wherein:

A is selected from the group consisting of C_{1-6}alkoxy, aryl and
heteroaryl; in which said aryl is phenyl or napthyl; said heteroaryl is selected
from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, furanyl,
15 thienyl, pyrrolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl,
quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, benzoimidazolyl and
benzothiazolyl; and said aryl or heteroaryl is optionally substituted with one
or two of the same or different amino, nitro, cyano, C_{1-6}alkoxy, -C(O)NH$_2$,
halogen or trifluoromethyl;

20

-W- is

25 - - may represent a carbon-carbon bond;

R^1 is hydrogen;

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R^2, R^3, R^4, and R^5 are each independently selected from the group (a)-(r) consisting of:

(a) hydrogen,

5   (b) halogen,

(c) cyano,

(d) nitro,

(e) amino,

(f) C_{1-4}alkylamino,

10   (g) di(C_{1-4}alkyl)amino,

(h) hydroxy,

(i) C_{1-6}alkyl optionally substituted with one to three same or different halogen, hydroxy, C_{1-6}alkoxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, cyano or nitro,

15   (j) C_{3-7}cycloalkyl optionally substituted with one to three same or different halogen, hydroxy, C_{1-6}alkoxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, cyano or nitro,

(k) C_{1-6}alkoxy,

(l) -C(O)OR^7,

20   (m) -C(O)R^8,

(n) -C(O)NR^{9}R^{10},

(o) -C(=NR^{12})(R^{11}),

(p) aryl, said aryl is phenyl or napthyl, and said aryl is optionally substituted with one to two of the same or different amino,

25   C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, cyano, C-amido, N-amido, C_{1-6}alkoxy, C_{1-6}thioalkoxy or halogen,

(q) heteroaryl, said heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl,

30   isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl and triazolyl, and said heteroaryl is optionally substituted with one to two same or different groups selected from (aa)-(pp) consisting of: (aa) halogen,

35   (bb) C_{1-6}alkyl, said C_{1-6}alkyl optionally substituted with one to three same or different halogen, hydroxy, cyano, amino, C_{1-4}alkylamino or di(C_{1-4}alkyl)amino, (cc) C_{3-6}alkenyl, (dd) C_{1-6}alkoxy, (ee) phenyl optionally substituted with one or two same or different halogen,

(ff) heteroaryl, said heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, furanyl, thienyl, oxazolyl, isoxazolyl, pyrazolyl, triazolyl and tetrazolyl, and said heteroaryl optionally substituted with one or two same or different C_{1-4}alkyl, C_{1-4}alkoxy, halogen, amino, C_{1-4}alkylamino and di(C_{1-4}alkyl)amino, (gg) heteroarylC_{1-6}alkyl-, in which the heteroaryl of said heteroaryl C_{1-6}alkyl- is selected from the group consisting of pyridinyl, furanyl, thienyl and pyrazolyl, the heteroaryl of said heteroarylC_{1-6}alkyl- is optionally substituted with one or two same or different C_{1-4}alkyl, halogen or amino, and in which a carbon of the C_{1-6}alkyl of said heteroarylC_{1-6}alkyl- is optionally replaced by one sulfur or sulfonyl, (hh) amino, (ii) C_{1-4}alkylamino, in which the C_{1-4}alkyl of said C_{1-4}alkylamino is optionally substituted with amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, morpholinyl, piperazinyl or piperidinyl, (jj) di (C_{1-4}alkyl)amino, (kk) C_{3-7}cycloalkylamino, (ll) -$(CH_2)_q{}^aC(O)R^{23}$, (mm) -$CH_2OC(O)C_{1-6}$alkyl, (nn) -NH-$(CH_2)_q{}^bC(O)R^{24}$, (oo) -$CO_2CH_2C(O)R^{25}$, (pp) phenylmethyl, in which the phenyl of said phenylmethyl is optionally substituted with a -$(CH_2)_q{}^cC(O)R^{26}$; and

(r) heteroalicyclic, said heteroalicyclic selected from the group consisting of piperazinyl, piperidinyl, morpholinyl, 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, 4,5-dihydro-thiazol-2-yl, 5-oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl and 4,5-dihydro-1H-imidazol-2-yl, and said heteroalicyclic is optionally substituted with one or two same or different C_{1-4}alkyl, C_{1-4}alkoxy, hydroxy, cyano or amino;

R^6 and R^7 are each independently selected from hydrogen or C_{1-6} alkyl;

R^8 is selected from the group consisting of C_{1-6}alkyl, phenyl and heteroaryl in which said heteroaryl is selected from the group consisting of oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, and pyrimidinyl and said heteroaryl is optionally substituted with one to two of the same or different C_{1-6}alkyl, amino, CO_2H or CO_2C_{1-6}alkyl;

R^9 and R^{10} are each independently selected from the group (a)-(l) consisting of:
(a) hydrogen,

(b) C_{1-6}alkyl, said C_{1-6}alkyl is optionally substituted with in one to two of the same or different amino, di(C_{1-6}alkyl)amino or C_{1-6}alkoxy,

(c) C_{1-6}alkoxy,

. (d) heteroaryl, in which said heteroaryl is selected from the group consisting of pyridinyl, isoxazolyl, benzoimidazolyl, tetrazolyl, pyrazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, benzothiazolyl, pyrimidinyl and isoquinolinyl and said heteroaryl is optionally substituted with one to two of the same or different C_{1-6}alkyl or C_{1-6}alkoxy,

(e) heteroaryl-C_{1-6}alkyl-, in which said heteroaryl is selected from the group consisting of indolyl, imidazolyl, benzoimidazolyl, pyridinyl, pyrimidinyl, thiazolyl, triazolyl, tetrazolyl, furanyl and thienyl,

(f) heteroalicyclic, in which said heteroalicyclic is morpholinyl, piperazinyl or dihydrothiazolyl, and said heteroalicyclic is optionally substituted with a C_{1-6}alkoxycarbonyl,

(g) morpholin-4-ylethyl,

(h) phenylsulfonyl,

(i) C_{1-4}alkylsulfonyl,

(j) amino,

(k) (C_{1-6}alkoxy)-C(O)NH-, and

(l) (C_{1-6}alkyl)-NHC(O)NH; or R^9 and R^{10} taken together with the nitrogen to which they are attached are 4-benzylpiperazin-1-yl or 4-benzoylpiperazin-1-yl;

R^{11} is selected from the group consisting of hydrogen, C_{1-6}alkoxy and $NR^{21}R^{22}$;

R^{12} is selected from the group consisting of hydrogen, hydroxy, $NHCO_2$ C_{1-6}alkyl and C_{1-6}alkoxy, said C_{1-6}alkoxy optionally substituted with one CO_2H or CO_2C_{1-6}alkyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} are each independently selected from hydrogen or C_{1-6}alkyl;

R^{21} and R^{22} are each independently selected from the group consisting of hydrogen, amino, C_{1-6}alkyl, C_{3-7}cycloalkyl and $NHCO_2C_{1-6}$alkyl;

R^{23}, R^{24}, R^{25} and R^{26} are each independently selected from the group consisting of hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy optionally substituted with morpholin-4-yl or di(C_{1-4}alkyl)amino, amino, pyrolidin-1-yl, (C_{1-4}alkyl)amino and di(C_{1-4}alkyl)amino;

q^a, q^b and q^c are each independently 0 or 1; and

provided that at least one of R^2, R^3, R^4, and R^5 is selected from the group consisting of -C(O)R^8, -C(O)NR^{9}R^{10}, -C(=NR^{12})(R^{11}), aryl, heteroaryl, and heteroalicyclic when - - represents a carbon-carbon bond.

2.   A compound of claim 1, including pharmaceutically acceptable salts thereof, wherein:

A is selected from the group consisting of C_{1-6}alkoxy, phenyl and heteroaryl in which said heteroaryl is selected from pyridinyl, furanyl and thienyl, and said phenyl or said heteroaryl is optionally substituted with one to two of the same or different amino, nitro, cyano, C_{1-6}alkoxy, -C(O)NH$_2$, halogen or trifluoromethyl;

- - represents a carbon-carbon bond;

R^6 is hydrogen;

R^{13}, R^{14}, R^{16}, R^{17} and R^{18} are each hydrogen; and

R^{15}, R^{19} and R^{20} are each independently hydrogen or C_{1-6}alkyl.

3.   A compound of claim 2, including pharmaceutically acceptable salts thereof, wherein:
        R^2 is selected from the group consisting of hydrogen, halogen and C_{1-6}alkoxy;
        R_3 and R_4 are hydrogen; and
        R^5 is selected from the group consisting of: -C(O)R^8, -C(O)NR^{9}R^{10}, -C(=NR^{12})(R^{11}), aryl, heteroaryl and heteroalicyclic.

4.   A compound of claim 3, including pharmaceutically acceptable salts thereof, wherein:

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R^2 is halogen or C_{1-6}alkoxy;

R^5 is phenyl, said phenyl optionally substituted with a C_{1-4}alkoxy, C_{1-4}thioalkoxy or halogen;

R^{15} and R^{19} are each hydrogen;

R^{20} is hydrogen or methyl; and

A is phenyl.

5.   A compound of claim 4, including pharmaceutically acceptable salts thereof, wherein:

R^2 is fluoro or methoxy;

R^5 is phenyl, said phenyl optionally substituted with a methoxy, thiomethoxy, or fluoro; and

R^{20} is hydrogen.

6.   A compound of claim 3, including pharmaceutically acceptable salts thereof, wherein:

R^2 is halogen or C_{1-6}alkoxy;

R^5 is selected from the group consisting of $-C(O)NR^9R^{10}$, $-C(=NR^{12})(R^{11})$ and heteroaryl in which said heteroaryl is tetrazolyl or oxadiazolyl and said heteroaryl is optionally substituted with one to two C_{1-6}alkyl, dihalomethyl, trihalomethyl or halogen;

R^{15} and R^{19} are each hydrogen;

R^{20} is hydrogen or C_{1-6} alkyl; and

A is heteroaryl, said heteroaryl selected from the group consisting of pyridinyl, furanyl and thienyl and said heteroaryl optionally substituted with a halogen.

7.   A compound of claim 6, including pharmaceutically acceptable salts thereof, wherein:

R^2 is fluoro

R^5 is selected from the group consisting of 2H-tetrazolyl, 2-dihalomethyl-2H-tetrazolyl, [1,2,4]-oxadiazolyl, 5-amino-[1,2,4]-oxadiazolyl, 5-trihalomethyl-[1,2,4]-oxadiazolyl, $-C(O)NH_2$ and $-C(=NOH)NH_2$;

R^{20} is hydrogen or methyl; and

A is pyridinyl.

8.   A compound of claim 6, including pharmaceutically acceptable salts thereof, wherein:

R^2 is fluoro;

5   R^5 is 2H-tetrazolyl or 2-methyl-2H-tetrazolyl;

R^{20} is hydrogen; and

A is furanyl or thienyl, in which said furanyl is optionally substituted with a chloro or bromo.

10   9.   A compound of claim 3, including pharmaceutically acceptable salts thereof, wherein:

R^2 is selected from the group consisting of hydrogen, fluoro or methoxy;

R^5 is -C(O)NR^{9}R^{10};

15   R^{15} and R^{19} are each hydrogen;

R^{20} is hydrogen or methyl; and

A is phenyl.

10.   A compound of claim 9, including pharmaceutically acceptable salts
20   thereof, wherein:

R^2 is hydrogen; and

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl optionally substituted with a di(C_{1-4}alkyl)amino, methylsulfonyl, phenylsulfonyl, and tetrazolyl, or R^9 and R^{10} taken
25   together with the nitrogen to which they are attached are 4-benzylpiperazin-1-yl.

11.   A compound of claim 9, including pharmaceutically acceptable salts thereof, wherein:

30   R^2 is methoxy;

R^{20} is hydrogen; and

R^9 and R^{10} are each independently hydrogen or methyl.

35   12.   A compound of claim 9, including pharmaceutically acceptable salts thereof, wherein:

R^2 is fluoro;

R^{20} is methyl; and

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, C_{1-6}alkyl and morpholin-4-ylethyl.

13. A compound of claim 9, including pharmaceutically acceptable salts thereof, wherein:

R^2 is fluoro; and

R^{20} is hydrogen.

14. A compound of claim 3, including pharmaceutically acceptable salts thereof,

wherein:

R^2 is hydrogen, methoxy or fluoro;

R^5 is $-C(O)R^8$;

R^{15} and R^{19} are each hydrogen;

R^{20} is hydrogen or methyl; and

A is phenyl.

15. A compound of claim 14, including pharmaceutically acceptable salts thereof, wherein:

R^2 is methoxy or fluoro; and

R^8 is C_{1-6}alkyl.

16. The compound of claim 15, including pharmaceutically acceptable salts thereof, wherein:

R^2 is methoxy;

R^8 is methyl; and

R^{20} is hydrogen.

17. A compound of claim 3, including pharmaceutically acceptable salts thereof, wherein:

R^2 is selected from the group consisting of hydrogen, methoxy and halogen;

R^5 is heteroaryl;

R^{15} and R^{19} are each hydrogen;

R^{20} is hydrogen or methyl; and

A is phenyl, said phenyl optionally substituted with one to two of the same or different cyano, fluoro, trifluoromethyl, amino, nitro, and $C(O)NH_2$.

18. A compound of claim 17, including pharmaceutically acceptable salts thereof, wherein:

R^5 is heteroaryl, said heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, oxazolyl, benzooxazolyl, imidazolyl, benzoimidazolyl, oxadiazolyl, pyrazolyl, triazolyl, tetrazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, and 1H-imidazo[4,5-c]pyridin-2-yl.

19. A compound of claim 3, including pharmaceutically acceptable salts thereof, wherein:

R^2 is selected from the group consisting of hydrogen, methoxy and fluoro;

R^5 is heteroalicyclic, said heteroalicyclic selected from the group consisting of 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, 4,5-dihydro-thiazol-2-yl, 5-oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl and 4,5-dihydro-1H-imidazol-2-yl;

R^{15} and R^{19} are each hydrogen;

R^{20} is hydrogen or methyl; and

A is phenyl.

20. A compound of claim 3, including pharmaceutically acceptable salts thereof, wherein:

R^2 is selected from the group consisting of hydrogen, methoxy and fluoro;

R^5 is -C(=NR^{12})(R^{11});

A is phenyl or C_{1-6}alkoxy;

R^{11} is selected from the group consisting of hydrogen, hydroxy, $NHCO_2C(CH_3)_3$ and OCH_2CO_2H; and

R^{12} is selected from the group consisting of hydrogen, ethoxy and $NR^{21}R^{22}$;

R^{15} and R^{19} are each hydrogen;

R^{20} is hydrogen or methyl;

R^{21} and R^{22} are each independently selected from the group consisting of hydrogen, amino, C_{1-6}alkyl, cyclopropyl and $NHCO_2C(CH_3)_3$.

21. A compound of claim 5, including pharmaceutically acceptable salts thereof, selected from the group consisting of:

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1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-phenyl-1H-indol-3-yl)-
ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(2-methylsulfanyl-phenyl)-
1H-indol-3-yl]-ethane-1,2-dione;

5   1-(4-Benzoyl-piperazin-1-yl)-2-[7-(4-fluoro-phenyl)-4-methoxy-1H-
indol-3-yl]-ethane-1,2-dione;

and 1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(4-methoxy-phenyl)-1H-
indol-3-yl]-ethane-1,2-dione.

10 22. A compound of claim 7, including pharmaceutically acceptable salts
thereof, selected from the group consisting of:

1-[4-Fluoro-7-(2H-tetrazol-5-yl)-1H-indol-3-yl]-2-[4-(pyridine-2-
carbonyl)-piperazin-1-yl]-ethane-1,2-dione;

15   1-[4-Fluoro-7-(2H-tetrazol-5-yl)-1H-indol-3-yl]-2-[2-(R)-methyl-4-
(pyridine-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione;

1-[7-(2-Difluoromethyl-2H-tetrazol-5-yl)-4-fluoro-1H-indol-3-yl]-2-[4-
(pyridine-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione;

4-Fluoro-N-hydroxy-3-{2-oxo-2-[4-(pyridine-2-carbonyl)-piperazin-1-yl]-
20   acetyl}-1H-indole-7-carboxamidine;

4-Fluoro-3-{2-oxo-2-[4-(pyridine-2-carbonyl)-piperazin-1-yl]-acetyl}-1H-
indole-7-carboxylic acid amide;

4-Fluoro-N-hydroxy-3-{2-[2-(R)-methyl-4-(pyridine-2-carbonyl)-
piperazin-1-yl]-2-oxo-acetyl}-1H-indole-7-carboxamidine;

25   4-Fluoro-3-{2-[2-(R)-methyl-4-(pyridine-2-carbonyl)-piperazin-1-yl]-2-
oxo-acetyl}-1H-indole-7-carboxylic acid amide;

1-[4-Fluoro-7-(5-trichloromethyl-[1,2,4]oxadiazol-3-yl)-1H-indol-3-yl]-2-
[2-(R)-methyl-4-(pyridine-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione;

1-[4-Fluoro-7-(5-trichloromethyl-[1,2,4]oxadiazol-3-yl)-1H-indol-3-yl]-2-
30   [4-(pyridine-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione;

1-[7-(5-Amino-[1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-2-[4-
(pyridine-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione;

1-[7-(5-Amino-[1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-2-[2-(R)-
methyl-4-(pyridine-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione;

35   1-(4-Fluoro-7-[1,2,4]oxadiazol-3-yl-1H-indol-3-yl)-2-[4-(pyridine-2-
carbonyl)-piperazin-1-yl]-ethane-1,2-dione; and

1-(4-Fluoro-7-[1,2,4]oxadiazol-3-yl-1H-indol-3-yl)-2-[2-(R)-methyl-4-
(pyridine-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione.

23. A compound of claim 8, including pharmaceutically acceptable salts thereof, selected from the group consisting of:

5   1-[4-Fluoro-7-(2H-tetrazol-5-yl)-1H-indol-3-yl]-2-[4-(furan-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione;

1-[4-(5-Chloro-furan-2-carbonyl)-piperazin-1-yl]-2-[4-fluoro-7-(2H-tetrazol-5-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-[4-(5-Bromo-furan-2-carbonyl)-piperazin-1-yl]-2-[4-fluoro-7-(2H-

10   tetrazol-5-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-[4-Fluoro-7-(2H-tetrazol-5-yl)-1H-indol-3-yl]-2-[4-(thiophene-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione;

1-[4-Fluoro-7-(2-methyl-2H-tetrazol-5-yl)-1H-indol-3-yl]-2-[4-(furan-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione;

15   1-[4-(5-Chloro-furan-2-carbonyl)-piperazin-1-yl]-2-[4-fluoro-7-(2-methyl-2H-tetrazol-5-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-[4-(5-Bromo-furan-2-carbonyl)-piperazin-1-yl]-2-[4-fluoro-7-(2-methyl-2H-tetrazol-5-yl)-1H-indol-3-yl]-ethane-1,2-dione; and

1-[4-Fluoro-7-(2-methyl-2H-tetrazol-5-yl)-1H-indol-3-yl]-2-[4-

20   (thiophene-2-carbonyl)-piperazin-1-yl]-ethane-1,2-dione.

24. A compound of claim 10, including pharmaceutically acceptable salts thereof, selected from the group consisting of:

25   N-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-1H-indole-7-carbonyl}-methanesulfonamide;

N-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-1H-indole-7-carbonyl}-benzenesulfonamide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-1H-indole-7-carboxylic

30   acid (1H-tetrazol-5-yl)-amide;

3-[2-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]-1H-indole-7-carboxylic acid methylamide;

3-[2-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]-1H-indole-7-carboxylic acid dimethylamide;

35   3-[2-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]-1H-indole-7-carboxylic acid (2-diethylamino-ethyl)-amide;

3-[2-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]-1H-indole-7-carboxylic acid ethylamide; and

1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-[7-(4-benzyl-piperazine-1-carbonyl)-1H-indol-3-yl]-ethane-1,2-dione.

25.   A compound of claim 11, including pharmaceutically acceptable salts thereof selected from:

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-methoxy-1H-indole-7-carboxylic acid methylamide; or
3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-methoxy-1H-indole-7-carboxylic acid amide.

26.   A compound of claim 12, including pharmaceutically acceptable salts thereof, selected from the group consisting of:

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (2-dimethylaminoethyl)-amide;
3-[2-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (2-morpholin-4-yl-ethyl)-amide; and
3-[2-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid amide.

27.   The compound of claim 13, including pharmaceutically acceptable salts thereof, selected from the group consisting of:

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid pyridin-3-ylamide;
3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (4,5-dihydro-thiazol-2-yl)-amide;
3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (3-methyl-isoxazol-5-yl)-amide;
3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid pyridin-2-ylamide;
3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid pyridin-4-ylamide;
N-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carbonyl}-benzenesulfonamide;
3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (1H-benzoimidazol-2-yl)-amide;

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3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid amide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (2-dimethylaminoethyl)-amide;

5   3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid benzylamide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid methoxy-amide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-

10   carboxylic acid methylamide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid [2-(1H-indol-3-yl)-ethyl]-amide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid [2-(1H-imidazol-4-yl)-ethyl]-amide;

15   3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (furan-2-ylmethyl)-amide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (thiophen-2-ylmethyl)-amide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-

20   carboxylic acid (2-morpholin-4-yl-ethyl)-amide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (1H-benzoimidazol-2-ylmethyl)-amide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (2H-tetrazol-5-yl)-amide;

25   3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (2H-pyrazol-3-yl)-amide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid isoxazol-3-ylamide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-

30   carboxylic acid thiazol-2-ylamide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid [1,3,4]thiadiazol-2-ylamide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid benzothiazol-2-ylamide;

35   N-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carbonyl}-methanesulfonamide;

1-[7-(4-Benzoyl-piperazine-1-carbonyl)-4-fluoro-1H-indol-3-yl]-2-(4-benzoyl-piperazin-1-yl)-ethane-1,2-dione;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (2,2-dimethoxyethyl)-amide;

N'-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carbonyl}-hydrazinecarboxylic acid tert-butyl ester;

5   3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid hydrazide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (2-methoxy-ethyl)-amide;

[2-({3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-

10   carbonyl}-amino)-ethyl]-carbamic acid tert-butyl ester;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (2-amino-ethyl)-amide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (2,6-dimethyl-pyrimidin-4-yl)-amide;

15   3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (6-methoxy-benzothiazol-2-yl)-amide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (5-methyl-thiazol-2-yl)-amide;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-

20   carboxylic acid (5-tert-butyl-thiazol-2-yl)-amide; and

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid isoquinolin-1-ylamide.

28.   The compound of claim 17, including pharmaceutically acceptable
25   salts thereof, selected from the group consisting of:

1-(4-Benzoyl-piperazin-1-yl)-2-[7-(5-chloro-thiophen-2-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(2-methyl-2H-tetrazol-5-yl)-

30   1H-indol-3-yl]-ethane-1,2-dione;

5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-tetrazol-2-yl)-acetic acid methyl ester;

1-(4-Benzoyl-piperazin-1-yl)-2-[7-(2-ethyl-2H-tetrazol-5-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

35   1-(4-Benzoyl-piperazin-1-yl)-2-[7-(2-propyl-2H-tetrazol-5-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[7-(2-benzyl-2H-tetrazol-5-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

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1-(4-Benzoyl-piperazin-1-yl)-2-[7-(2-allyl-2H-tetrazol-5-yl)-4-fluoro-1H-
indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-methoxy-[1,2,4]oxadiazol-
3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

5   (5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-
yl}-tetrazol-2-yl)-acetic acid;

(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-
yl}-tetrazol-2-yl)-N-methyl-acetamide;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-methyl-2H-[1,2,4]triazol-3-
10   yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-(5-methyl-[1,2,4]oxadiazol-3-
yl)-1H-indol-3-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-(5-trichloromethyl-
[1,2,4]oxadiazol-3-yl)-1H-indol-3-yl)-ethane-1,2-dione;

15   1-(4-Benzoyl-piperazin-1-yl)-2-[7-(5-cyclopropylamino-
[1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[7-(5-amino-[1,2,4]oxadiazol-3-yl)-4-
fluoro-1H-indol-3-yl]-ethane-1,2-dione;

1-[7-(3-Benzoyl-3H-imidazol-4-yl)-4-fluoro-1H-indol-3-yl]-2-(4-benzoyl-
20   piperazin-1-yl)-ethane-1,2-dione;

5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-
1H-pyrazole-3-carboxylic acid ethyl ester;

5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-
isoxazole-3-carboxylic acid ethyl ester;

25   5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-
1H-pyrazole-3-carboxylic acid;

5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-
1H-pyrazole-3-carboxylic acid methylamide;

1-[7-(5-Amino-[1,3,4]oxadiazol-2-yl)-4-fluoro-1H-indol-3-yl]-2-(4-
30   benzoyl-piperazin-1-yl)-ethane-1,2-dione;

N-(3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-
yl}-[1,2,4]oxadiazol-5-yl)-acetamide;

1-(4-Benzoyl-piperazin-1-yl)-2-[7-(5-chloromethyl-[1,2,4]oxadiazol-3-
yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

35   (3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-
yl}-[1,2,4]oxadiazol-5-yl)-acetic acid methyl ester;

2-(3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-
yl}-[1,2,4]oxadiazol-5-yl)-N-methyl-acetamide;

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(3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-[1,2,4]oxadiazol-5-yl)-acetic acid;

3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-[1,2,4]oxadiazole-5-carboxylic acid methyl ester;

5   3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-[1,2,4]oxadiazole-5-carboxylic acid methylamide;

3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-[1,2,4]oxadiazole-5-carboxylic acid amide;

2-(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-

10   yl}-tetrazol-2-yl)-acetamide;

3-(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-tetrazol-2-ylmethyl)-benzoic acid methyl ester;

3-(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-tetrazol-2-ylmethyl)-benzoic acid;

15   3-(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-tetrazol-2-ylmethyl)-benzamide;

2-(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-tetrazol-2-ylmethyl)-benzoic acid methyl ester;

2-(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-

20   yl}-tetrazol-2-ylmethyl)-benzoic acid;

2-(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-tetrazol-2-ylmethyl)-benzamide;

4-(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-tetrazol-2-ylmethyl)-benzoic acid methyl ester;

25   4-(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-tetrazol-2-ylmethyl)-benzoic acid;

4-(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-tetrazol-2-ylmethyl)-benzamide;

Acetic acid 5-{3-[2-(4-benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-

30   1H-indol-7-yl}-tetrazol-2-yl methyl ester;

2,2-Dimethyl-propionic acid 5-{3-[2-(4-benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-tetrazol-2-yl methyl ester;

1-(4-Benzoyl-piperazin-1-yl)-2-{4-fluoro-7-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl]-1H-indol-3-yl}-ethane-1,2-dione;

35   2-[2-(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-tetrazol-2-yl)-ethyl]-isoindole-1,3-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-{7-[2-(2-diethylamino-ethyl)-2H-tetrazol-5-yl]-4-fluoro-1H-indol-3-yl}-ethane-1,2-dione;

4-(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-tetrazol-2-yl)-butyronitrile;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-pyridin-4-yl-4H-[1,2,4]triazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

5   1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-pyridin-3-yl-4H-[1,2,4]triazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

(5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-4H-[1,2,4]triazol-3-yl)-acetonitrile;

5-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-

10   4H-[1,2,4]triazole-3-carboxylic acid amide;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-pyrazin-2-yl-4H-[1,2,4]triazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-4H-[1,2,4,5]tetrazine-1-carboxylic acid tert-butyl ester;

15   1-[7-(5-Aminomethyl-[1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-2-(4-benzoyl-piperazin-1-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-methylaminomethyl-[1,2,4]oxadiazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-dimethylaminomethyl-

20   [1,2,4]oxadiazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-hydroxymethyl-[1,2,4]oxadiazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

(3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-[1,2,4]oxadiazol-5-ylamino)-acetic acid methyl ester;

25   (3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-[1,2,4]oxadiazol-5-ylamino)-acetic acid;

2-(3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-[1,2,4]oxadiazol-5-ylamino)-acetamide;

2-(3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-

30   yl}-[1,2,4]oxadiazol-5-ylamino)-N-methyl-acetamide;

(3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-[1,2,4]triazol-1-yl)-acetic acid methyl ester;

2-(3-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-[1,2,4]triazol-1-yl)-N-methyl-acetamide;

35   2-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-1H-imidazole-4-carboxylic acid methyl ester;

2-{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-1H-imidazole-4-carboxylic acid methylamide;

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1-[7-(5-Amino-[1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-2-(4-
benzoyl-2-methyl-piperazin-1-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[7-(5-dimethylamino-[1,2,4]oxadiazol-3-
yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

5   1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-methylamino-
[1,2,4]oxadiazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-isopropylamino-
[1,2,4]oxadiazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-{4-fluoro-7-[5-(2-

10   morpholin-4-yl-ethylamino)-[1,2,4]oxadiazol-3-yl]-1H-indol-3-yl}-
ethane-1,2-dione;

1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-[7-(5-sec-butylamino-
[1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-[7-(5-cyclobutylamino-

15   [1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-[7-(5-cyclopentylamino-
[1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-[4-fluoro-7-(2-methyl-2H-
tetrazol-5-yl)-1H-indol-3-yl]-ethane-1,2-dione;

20   1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-[4-fluoro-7-(5-methyl-
[1,2,4]oxadiazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-[7-(5-cyclopropyl-
[1,2,4]oxadiazol-3-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-[4-fluoro-7-(5-

25   trifluoromethyl-[1,2,4]oxadiazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-(4-fluoro-7-
[1,2,4]oxadiazol-3-yl-1H-indol-3-yl)-ethane-1,2-dione;

3-{3-[2-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-
1H-indol-7-yl}-[1,2,4]oxadiazole-5-carboxylic acid methyl ester;

30   1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-trichloromethyl-
[1,3,4]oxadiazol-2-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[7-(5-chloromethyl-1H-[1,2,4]triazol-3-
yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione; and

1-(4-Benzoyl-piperazin-1-yl)-2-{4-fluoro-7-[3-(furan-2-

35   ylmethanesulfonylmethyl)-[1,2,4]oxadiazol-5-yl]-1H-indol-3-yl}-ethane-
1,2-dione;

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1-(4-Benzoyl-piperazin-1-yl)-2-{4-fluoro-7-[3-(thiophen-2-
ylsulfanylmethyl)-[1,2,4]oxadiazol-5-yl]-1H-indol-3-yl}-ethane-1,2-
dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(3-phenyl-[1,2,4]oxadiazol-5-
5   yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-{4-fluoro-7-[3-(pyridin-2-
ylsulfanylmethyl)-[1,2,4]oxadiazol-5-yl]-1H-indol-3-yl}-ethane-1,2-
dione;

1-(4-Benzoyl-piperazin-1-yl)-2-{4-fluoro-7-[3-(4-fluoro-phenyl)-
10   [1,2,4]oxadiazol-5-yl]-1H-indol-3-yl}-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-{4-fluoro-7-[3-(2-oxo-2-pyrrolidin-1-yl-
ethyl)-[1,2,4]oxadiazol-5-yl]-1H-indol-3-yl}-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[7-(3-benzyl-[1,2,4]oxadiazol-5-yl)-4-
fluoro-1H-indol-3-yl]-ethane-1,2-dione;

15   1-(4-Benzoyl-piperazin-1-yl)-2-{4-fluoro-7-[3-(5-methyl-isoxazol-3-yl)-
[1,2,4]oxadiazol-5-yl]-1H-indol-3-yl}-ethane-1,2-dione; and

1-(4-Benzoyl-piperazin-1-yl)-2-(7-{3-[2-(3,5-dimethyl-pyrazol-1-yl)-
ethyl]-[1,2,4]oxadiazol-5-yl}-4-fluoro-1H-indol-3-yl)-ethane-1,2-dione.

20   29.   The compound of claim 18, including pharmaceutically acceptable
        salts thereof, selected from the group consisting of:

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-pyridin-2-yl-1H-indol-3-yl)-
ethane-1,2-dione;

25   1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-pyridin-2-yl-1H-indol-3-yl)-
ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-methoxy-7-pyridin-3-yl-1H-indol-3-
yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-methoxy-7-pyridin-3-yl-1H-indol-3-
30   yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-pyrimidin-5-yl-1H-indol-3-yl)-
ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-methoxy-7-pyrimidin-5-yl-1H-indol-3-
yl)-ethane-1,2-dione;

35   1-(4-Benzoyl-piperazin-1-yl)-2-(7-furan-2-yl-4-methoxy-1H-indol-3-yl)-
ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-thiophen-2-yl-1H-indol-3-yl)-
ethane-1,2-dione;

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1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-thiophen-3-yl-1H-indol-3-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-thiazol-2-yl-1H-indol-3-yl)-ethane-1,2-dione;

5   1-(4-Benzoyl-piperazin-1-yl)-2-(4-methoxy-7-thiazol-2-yl-1H-indol-3-yl)-ethane-1,2-dione

1-(4-Benzoyl-piperazin-1-yl)-2-[7-(5-chloro-thiophen-2-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-oxazol-5-yl-1H-indol-3-yl)-

10   ethane-1,2-dione;

1-(7-Benzooxazol-2-yl-4-fluoro-1H-indol-3-yl)-2-(4-benzoyl-piperazin-1-yl)-ethane-1,2-dione;

1-(7-Benzo[b]thiophen-2-yl-4-methoxy-1H-indol-3-yl)-2-(4-benzoyl-piperazin-1-yl)-ethane-1,2-dione;

15   1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(2H-tetrazol-5-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-[4-fluoro-7-(2H-tetrazol-5-yl)- -indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-oxazol-2-yl-1H-indol-3-yl)-

20   ethane-1,2-dione;

1-[7-(1H-Benzoimidazol-2-yl)-4-fluoro-1H-indol-3-yl]-2-(4-benzoyl-piperazin-1-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-[1,2,4]oxadiazol-3-yl-1H-indol-3-yl)-ethane-1,2-dione;

25   1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(3H-imidazol-4-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-[1,3,4]oxadiazol-2-yl-1H-indol-3-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(1H-[1,2,4]triazol-3-yl)-1H-

30   indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-methoxy-7-(1H-[1,2,4]triazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-pyrazol-1-yl-1H-indol-3-yl)-ethane-1,2-dione;

35   1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-imidazol-1-yl-1H-indol-3-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-fluoro-7-[1,2,4]triazol-1-yl-1H-indol-3-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-(4-methoxy-7-[1,2,4]oxadiazol-3-yl-1H-indol-3-yl)-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(1H-imidazo[4,5-c]pyridin-2-yl)-1H-indol-3-yl]-ethane-1,2-dione; and

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(1H-imidazo[4,5-b]pyridin-2-yl)-1H-indol-3-yl]-ethane-1,2-dione.

30. A compound of claim 19, including pharmaceutically acceptable salts thereof, selected from the group consisting of:

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboxylic acid (4,5-dihydro-thiazol-2-yl)-amide;

1-(4-Benzoyl-piperazin-1-yl)-2-[4-fluoro-7-(5-oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-1H-indol-3-yl]-ethane-1,2-dione;

1-(4-Benzoyl-piperazin-1-yl)-2-[7-(4,5-dihydro-1H-imidazol-2-yl)-4-fluoro-1H-indol-3-yl]-ethane-1,2-dione; and

1-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-[4-fluoro-7-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-1H-indol-3-yl]-ethane-1,2-dione.

31. A compound of claim 20, including pharmaceutically acceptable salts thereof, selected from the group consisting of:

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-N-hydroxy-1H-indole-7-carboxamidine;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carbaldehyde oxime;

{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-ylmethyleneaminooxy}-acetic acid;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indole-7-carboximidic acid ethyl ester;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-N-cyclopropyl-4-fluoro-1H-indole-7-carboxamidine;

3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-N-amino-4-fluoro-1H-indole-7-carboxamidine;

N'-(Amino-{3-[2-(4-benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-yl}-methylene)-hydrazinecarboxylic acid tert-butyl ester;

N'-[{3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-1H-indol-7-
yl}-(tert-butoxycarbonyl-hydrazono)-methyl]-hydrazinecarboxylic acid
tert-butyl ester;
4-{2-[4-Fluoro-7-(N-hydroxycarbamimidoyl)-1H-indol-3-yl]-2-oxo-
5   acetyl}-piperazine-1-carboxylic acid tert-butyl ester;
3-[2-(4-Benzoyl-piperazin-1-yl)-2-oxo-acetyl]-4-methoxy-1H-indole-7-
carbaldehyde oxime; and
3-[2-(4-Benzoyl-2-(R)-methyl-piperazin-1-yl)-2-oxo-acetyl]-4-fluoro-N-
hydroxy-1H-indole-7-carboxamidine.
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32.   A pharmaceutical formulation which comprises an antiviral effective
amount of a compound of Formula I, including pharmaceutically
acceptable salts thereof, as claimed in any of claims 1-31, and a
pharmaceutically acceptable carrier, adjuvant or diluent.

15   33.   The pharmaceutical formulation of claim 32, useful for treating
infection by HIV, which additionally comprises an antiviral effective
amount of an AIDS treatment agent selected from the group
consisting of:

(a)   an AIDS antiviral agent;

20   (b)   an anti-infective agent;

(c)   an immunomodulator; and

(d)   HIV entry inhibitors.

34.   A method for treating mammals infected with a virus, comprising
25   administering to said mammal an antiviral effective amount of a

36.   The method of claim 34 wherein the virus is HIV.

37.   The method of claim 35 wherein the virus is HIV.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 403 /12; A61K 31 /496; A61P 3/ (X), 3 /12, 3/18
US CL : 544/ /387, 180, 242; 514 / 252.13, 241, 256

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/ /387, 180, 242; 514 / 252.13, 241, 256

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 00/76521 A1 (BRISTOL-MYERS SQUIBB COMPANY) 21 December 2000 (21.12.2000) See entire document.	1-35
A	US 5,424,329 A (BOSCHELLI et al.) 13 June 1995 (13.06.1955) See entire document.	1-35

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier application or patent published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 September 2001 (06.09.2001)	30 OCT 2001
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